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(22) International Filing Date: 19 November 1999 (19.11.99)		(74) Agent: SPIEGEL, Allen, J.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).	
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(71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).			
(71) Applicant (for all designated States except GB US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): BANKS, Bernard, Joseph [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). CROOK, Robert, James [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). GIBSON, Stephen, Paul [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). LUNN, Graham [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). PETTMAN, Alan, John [GB/GB]; Pfizer			

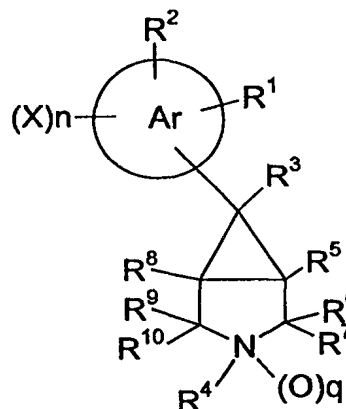
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(54) Title: 3-AZABICYCLO[3.1.0.] HEXANE DERIVATIVES AS OPIATE RECEPTORS LIGANDS

## (57) Abstract

Compounds of formula (I), their salts and prodrugs thereof, where the substituents are as defined herein are disclosed as opiate binding agents useful in the treatment of opiate-mediated conditions. Also described are processes for making such substances.



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## 3-AZABICYCLO[3.1.0.] HEXANE DERIVATIVES AS OPIATE RECEPTORS LIGANDS

This invention relates to pharmaceutically useful compounds, in particular compounds that bind to opiate receptors (e.g. mu, kappa and delta opioid receptors). Compounds that bind to such receptors are likely to be useful in the treatment of diseases modulated by opiate receptors, for example irritable bowel syndrome; constipation; nausea; vomiting; and pruritic dermatoses, such as allergic dermatitis and atopy in animals and humans. Compounds that bind to opiate receptors have also been indicated in the treatment of eating disorders, opiate overdoses, depression, smoking and alcohol addiction, sexual dysfunction, shock, stroke, spinal damage and head trauma.

There is a particular need for an improved treatment of itching. Itching, or pruritus, is a common dermatological symptom that can give rise to considerable distress in both humans and animals. Pruritus is often associated with inflammatory skin diseases which may be caused by hypersensitivity reactions, including reactions to insect bites, such as flea bites, and to environmental allergens, such as house dust mite or pollen; by bacterial and fungal infections of the skin; or by ectoparasite infections.

Existing treatments that have been employed in the treatment of pruritus include the use of corticosteroids and antihistamines. However, both of these treatments are known to have undesirable side effects. Other therapies that have been employed include the use of essential fatty acid dietary supplements, though these have the disadvantages of being slow to act, and of offering only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed, but with limited success.

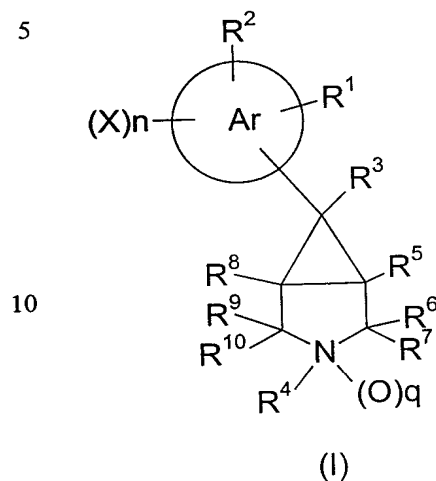
Thus, there is a continuing need for alternative and/or improved treatments of pruritus.

Certain 4-arylpiperidine-based compounds are disclosed in *inter alia* European patent applications EP 287339, EP 506468 and EP 506478 as opioid antagonists. In

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addition, International Patent Application WO 95/15327 discloses azabicycloalkane derivatives useful as neuroleptic agents.

According to the invention there is provided a compound of formula I,



15 wherein the "Ar" ring represents an optionally benzo-fused phenyl or 5- or 6-membered heteroaryl ring;

$R^1$  when taken alone is H, halogen,  $\text{NO}_2$ ,  $\text{NH}_2$ ,  $\text{NY}^2\text{WY}^1$ ,  $\text{Het}^1$ , AD,  $\text{CO}_2\text{R}^7$ ,  $\text{C(O)R}^8$ ,  $\text{C(=NOH)R}^8$ , or OE,

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$\text{Y}^2$  is H,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{3-6}$  alkenyl (each of which alkyl and alkenyl is optionally substituted by aryl, aryloxy or  $\text{Het}^1$ ),

W is  $\text{SO}_2$ , CO,  $\text{C(O)O}$ ,  $\text{P(Y}^1\text{)=O}$ ,  $\text{P(Y}^1\text{)=S}$ ,

25

$\text{Y}^1$  is  $\text{C}_{1-10}$  alkyl (optionally substituted by one or more substituents independently selected from halogen, OH,  $\text{C}_{1-4}$  alkoxy,  $\text{C}_{1-6}$  alkanoyloxy,  $\text{CONH}_2$ ,  $\text{C}_{1-6}$  alkoxycarbonyl,  $\text{NH}_2$ , aryl, mono- or di( $\text{C}_{1-4}$  alkyl)amino,  $\text{C}_{3-8}$  cycloalkyl, phthalimidyl,  $\text{Het}^1$ ),  $\text{Het}^1$ , aryl (optionally substituted by one or more substituents independently selected from  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl and halogen),  $\text{NH}_2$ ,  $\text{N(C}_{1-6}\text{ alkyl)}_2$  or  $\text{NH(C}_{1-6}\text{ alkyl)}$ ,

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Het<sup>1</sup> is a heterocyclic group containing up to 4 heteroatoms selected from N, O and S, which may comprise up to 3 rings (preferably a heteroaryl group, optionally benzo- or pyrido-fused heteroaryl), optionally substituted by one or more substituents independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>3-6</sub> halocycloalkyl, 5 =O, OH, halogen, NO<sub>2</sub>, SiR<sup>19a</sup>R<sup>19b</sup>R<sup>19c</sup>, CON<sup>20a</sup>R<sup>20b</sup>, NR<sup>20a</sup>R<sup>20b</sup>, SR<sup>21a</sup>, NR<sup>21b</sup>SO<sub>2</sub>R<sup>22a</sup>, NR<sup>21c</sup>C(O)OR<sup>22b</sup>, NR<sup>21d</sup>COR<sup>22d</sup>, and C<sub>1-6</sub> alkoxycarbonyl, and if a S atom is present in a ring, it can be present as part of a -S-, S(O)- or -S(O<sub>2</sub>)- group, and carbon atoms in the ring can be present as a part of a carbonyl moiety;

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R<sup>19a</sup>, R<sup>19b</sup>, R<sup>19c</sup> each independently represent C<sub>1-6</sub> alkyl or aryl,

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R<sup>20a</sup> and R<sup>20b</sup> each independently represent H, C<sub>1-6</sub> alkyl, aryl, (C<sub>1-4</sub> alkyl)phenyl, each of which alkyl, aryl and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen, or R<sup>20a</sup> and R<sup>20b</sup> can be taken together with the N atom to which they are attached, to form a 4- to 6-membered ring optionally substituted by one or more substituents independently selected from one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, =O, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen,

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R<sup>21a, b, c and d</sup> each independently represent H, C<sub>1-6</sub> alkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which alkyl, aryl, and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, halogen, NH<sub>2</sub>,

25

R<sup>22a, b and c</sup> each independently represent C<sub>1-6</sub> alkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which alkyl, aryl, and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, halogen, NH<sub>2</sub>,

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A is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene or C<sub>2-4</sub> alkynylene, each of which is optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogen and/or OH,

D is H, OH, CN, NR<sup>25</sup>R<sup>26</sup>, CONR<sup>25</sup>R<sup>26</sup>, NHR<sup>27</sup>, CO<sub>2</sub>R<sup>28</sup>, COR<sup>29</sup>, C(=NOH)R<sup>29</sup>,

or AD is CN, NR<sup>25</sup>R<sup>26</sup>, CONR<sup>25</sup>R<sup>26</sup>,

5 where R<sup>25</sup> and R<sup>26</sup> are either each independently H, C<sub>1-3</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl, C<sub>1-4</sub> alkylphenyl (each of which C<sub>1-3</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl and C<sub>1-4</sub> alkylphenyl are optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl and/or C<sub>1-4</sub> alkoxy, (each of which latter C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy is optionally substituted by one or more halogen)),

10 or R<sup>25</sup> and R<sup>26</sup> are taken together with the N atom to which they are attached and can form a 4- to 7-membered heterocyclic ring optionally incorporating one or more further hetero atoms selected from N, O and S, and which ring is optionally substituted by one or more C<sub>1-4</sub> alkyl, OH, =O, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen,

R<sup>27</sup> is COR<sup>30</sup>, CO<sub>2</sub>R<sup>31a</sup>, SO<sub>2</sub>R<sup>31b</sup>,

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R<sup>28</sup> and R<sup>29</sup> are each independently H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl and C<sub>1-4</sub> alkylphenyl are optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy (each of which latter C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy are optionally substituted by one or more  
20 halogen),

R<sup>30</sup> is H, C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, aryl, aryloxy, C<sub>1-4</sub> alkylphenyl, phenyl(C<sub>1-4</sub>)alkoxy, (each of which C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, aryl, aryloxy, C<sub>1-4</sub> alkylphenyl and phenyl(C<sub>1-4</sub>)alkoxy are  
25 optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy (which latter alkyl and alkoxy are optionally substituted by one or more halogen)),

R<sup>31a</sup> and R<sup>31b</sup> are each independently C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which is optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy, each of which latter alkyl and alkoxy is optionally substituted by  
30 one more halogen

E is H,  $\text{CONR}^{32}\text{R}^{33}$ ,  $\text{CSNR}^{32}\text{R}^{33}$ ,  $\text{COR}^{34}$ ,  $\text{CO}_2\text{R}^{34}$ ,  $\text{COCH}(\text{R}^{34a})\text{NH}_2$ ,  $\text{R}^{35}$ ,  $\text{CH}_2\text{CO}_2\text{R}^{35a}$ ,  $\text{CHR}^{35b}\text{CO}_2\text{R}^{35a}$ ,  $\text{CH}_2\text{OCO}_2\text{R}^{35c}$ ,  $\text{CHR}^{35d}\text{OCO}_2\text{R}^{35c}$ ,  $\text{COCR}^{36}=\text{CR}^{37}\text{NH}_2$ ,  $\text{COCHR}^{36}\text{CHR}^{37}\text{NH}_2$ , or  $\text{PO}(\text{OR}^{38})_2$ ,

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$\text{R}^{32}$  and  $\text{R}^{33}$  are each independently H,  $\text{C}_{3-10}$  alkylalkenyl,  $\text{C}_{3-7}$  cycloalkyl (optionally substituted by  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-10}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by  $\text{C}_{1-4}$  alkyl) or phenyl optionally substituted by  $(\text{X})_n$ ),

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or  $\text{R}^{32}$  and  $\text{R}^{33}$  can be taken together with the N atom to which they are attached and can form a 5- to 8-membered heterocycle optionally comprising further hetero atoms selected from N, O and S, which heterocycle is optionally substituted by  $\text{C}_{1-4}$  alkyl, optionally substituted by one or more halogen,

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$\text{R}^{34}$  is H,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH), or  $\text{C}_{1-6}$  alkyl (optionally substituted by one or more halogen,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), or phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH)),

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$\text{R}^{34a}$  is H,  $\text{C}_{1-6}$  alkyl (optionally substituted by one or more halogen,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), or phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH)),  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH) or a naturally occurring amino acid substituent,

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$\text{R}^{35}$  is  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl (optionally substituted by one or more  $(\text{X})_n$ ),  $\text{C}_{1-4}$  alkanoyl,  $\text{NHR}^{32}$ ,  $\text{CON}(\text{R}^{32})_2$ , and/or OH),  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl (optionally substituted by one or more  $(\text{X})_n$ ),  $\text{C}_{1-4}$

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alkanoyl,  $\text{NHR}^{32}$ ,  $\text{CON(R}^{32})_2$ , and/or OH)),  $\text{C}_{1-4}$  alkoxy( $\text{C}_{1-4}$  alkyl), phenyl( $\text{C}_{1-4}$ )alkyloxy( $\text{C}_{1-4}$ )alkyl, tetrahydropyranyl, tetrahydrofuranyl, cinnamyl or trimethylsilyl,

$\text{R}^{35a,b,c}$  and  $\text{d}$  are each independently H,  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl optionally substituted by one or more  $(\text{X})_n$  or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

$\text{R}^{36}$  and  $\text{R}^{37}$  each independently represent H,  $\text{C}_{3-6}$  alkylalkenyl,  $\text{C}_{4-7}$  cycloalkyl, phenyl optionally substituted by one or more  $(\text{X})_n$ , or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

$\text{R}^{38}$  is  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl optionally substituted by one or more  $(\text{X})_n$ , or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

$\text{R}^2$  when taken alone is H or halogen;

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or  $\text{R}^1$  and  $\text{R}^2$ , when attached to adjacent carbon atoms, can be taken together with the carbon atoms to which they are attached, and may represent  $\text{Het}^{1a}$ ;

$\text{Het}^{1a}$  is a heterocyclic group containing up to 4 heteroatoms selected from N, O and S, which may comprise up to 3 rings (and is preferably an optionally benzo-fused 5- to 7-membered heterocyclic ring) and which group is optionally substituted by one or more substituents independently selected from OH, =O, halogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy, which  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy groups can be optionally substituted by one or more  $\text{C}_{3-6}$  cycloalkyl, aryl( $\text{C}_{1-6}$ )alkyl, which aryl group is optionally substituted by one or more halogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy,

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which latter C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy and C<sub>1-4</sub> haloalkoxy groups can be optionally substituted by one or more NR<sup>23</sup>R<sup>24</sup>, NR<sup>23</sup>S(O)<sub>n</sub>R<sup>24</sup>, NR<sup>23</sup>C(O)<sub>m</sub>R<sup>24</sup>, and if a S atom is present in a ring, it can be present as part of a -S-, S(O)- or -S(O<sub>2</sub>)- group,

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which R<sup>23</sup> and R<sup>24</sup> when taken alone independently represent H, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> haloalkyl,

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or R<sup>23</sup> and R<sup>24</sup> can be taken together with the N atom to which they are attached, to form a 4- to 6-membered heterocyclic ring optionally comprising one or more further heteroatoms selected from, N, O, or S, and which heterocyclic ring is optionally substituted by one or more halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy and/or C<sub>1-4</sub> haloalkoxy groups,

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R<sup>3</sup> is H, CN, halogen, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl, aryloxy, heteroaryl, saturated heterocycle, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup>, NY<sup>2</sup>WY<sup>1</sup>, C<sub>1-6</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, (each of which alkyl, alkenyl and alkynyl groups is optionally substituted by one or more CN, halogen, OH, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkyloxy carbonyloxy, C<sub>1-6</sub> alkanoyl, C<sub>1-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl, aryloxy, heteroaryl, saturated heterocycle, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> and/or NY<sup>2</sup>WY<sup>1</sup>),

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R<sup>4</sup> is C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl or C<sub>3-10</sub> alkynyl each of which groups is linked to the N atom via a sp<sup>3</sup> carbon, and which is optionally substituted by one or more OH, CN, halogen, C<sub>1-6</sub> alkoxy (optionally substituted by aryl), aryloxy (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH and/or NY<sup>2</sup>WY), C<sub>1-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH and/or NY<sup>2</sup>WY), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY), heterocycle

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(optionally benzo-fused and optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, OH, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY), heterocycloxy (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, OH, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY), adamantyl or ZBNR<sup>14</sup>R<sup>15</sup>,

Z is a direct bond, CO or S(O)<sub>n</sub> group,

B is (CH<sub>2</sub>)<sub>p</sub>,

10

R<sup>12</sup> and R<sup>13</sup> each independently represent H or C<sub>1-4</sub> alkyl,

15

or R<sup>12</sup> and R<sup>13</sup> can be taken together with the N atom to which they are attached to form a 4- to 7-membered heterocycle optionally comprising a further hetero moiety selected from NR<sup>16</sup>, O and/or S, and which is optionally substituted by one or more C<sub>1-4</sub> alkyl,

20

R<sup>14</sup> and R<sup>15</sup> each independently represent H, C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl, C<sub>3-10</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, aryl or heteroaryl,

25

or R<sup>14</sup> and R<sup>15</sup> can be taken together with the N atom to which they are attached to form a 4- to 7-membered heterocycle optionally comprising a further hetero moiety selected from NR<sup>16</sup>, O and/or S, and which is optionally substituted by one or more C<sub>1-4</sub> alkyl,

R<sup>16</sup> is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, (C<sub>1-6</sub> alkylene)(C<sub>3-8</sub> cycloalkyl) or (C<sub>1-6</sub> alkylene)aryl,

30

R<sup>5</sup> and R<sup>8</sup> when taken separately are each independently H, C<sub>1-6</sub> alkyl,

R<sup>5</sup> and R<sup>8</sup> can be taken together with the carbon atoms to which they are joined to form a C<sub>3-8</sub> cycloalkyl ring,

R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup> and R<sup>10</sup> when taken separately are H,

R<sup>5</sup> and R<sup>6</sup> or R<sup>7</sup> can be taken together with the carbon atoms to which they are joined  
5 to form a C<sub>3-8</sub> cycloalkyl ring,

X is halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkyl or C<sub>1-4</sub> haloalkoxy,

m is 1 or 2;

10

n is 0, 1 or 2;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

15 q is 0 or 1;

"Naturally occurring amino acid substituent" means the  $\alpha$ -substituent that occurs in any one of the following natural amino acids, glycine, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, tyrosine, histidine, serine, threonine,  
20 methionine, cysteine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, arginine or proline;

"Heteroaryl" represents an aromatic ring containing up to four heteroatoms independently selected from N, O and S, and if a S atom is present in the ring, it can  
25 be present as part of a -S-, S(O)- or -S(O)<sub>2</sub>- group, and which may be joined to the remainder of the compound via any available atom(s);

"Heterocycle" is a group containing 1, 2 or 3 rings, and which contains up to 4 ring heteroatoms selected from N, O and S and up to 18 ring carbon atoms;

30

"Aryl", including in the definitions of "aryloxy", etc., means a group comprising a phenyl ring and which may incorporate a further carbocyclic ring fused to said phenyl

ring and which may be joined to the remainder of the compound via any available atom(s) (examples of such groups include naphthyl, indanyl, etc.);

5 "Alkyl", "alkenyl" and "alkynyl" groups can be linear or branched if the number of carbon atoms allows;

"Cycloalkyl" groups can be polycyclic if the number of carbon atoms allows;

10 or a pharmaceutically or veterinarily acceptable derivative or prodrug thereof.

Where a fused heterocyclic group is present it can be attached to the remainder of the compound via any available atom(s).

15 "Haloalkyl", "haloalkoxy" groups and the like can contain more than one halogen atom, and for instance can be per-halogenated.

Certain of the compounds of the invention can exist in one or more geometric and/or stereoisomeric forms. The present invention includes all such individual isomers and salts and prodrugs thereof.

20 Certain compounds of the present invention may exist in more than one tautomeric form. Similarly certain compounds of the invention may have zwitterionic forms. It is to be understood that the invention embraces all such tautomers, zwitterions and their derivatives.

25 The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, 30 methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the

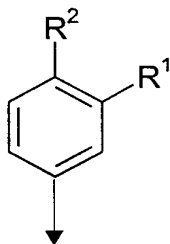


aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., **66**, 1-19 (1977).

- 5 It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be transformed after administration into or onto the body, for example by metabolism, to form compounds of formula (I) which are pharmacologically active. Such derivatives
- 10 are included in the term "prodrug". It will further be appreciated by those skilled in the art that certain moieties known to those skilled in the art as "pro-moieties", for example as described in "Design of Prodrugs" by H Bundgaard (Elsevier) 1985, may be placed on appropriate functionalities when such functionalities are present in compounds of formula (I), also to form a "prodrug". Further, certain compounds of
- 15 formula I may act as prodrugs of other compounds of formula I. All protected derivatives, and prodrugs, of the compounds of formula I are included within the scope of the invention.

Preferably the "Ar" ring represents phenyl or pyridyl.

- 20 Most preferably the "Ar" ring represents a group of formula:



25

Preferably R<sup>1</sup> when taken alone is OH, CN, halogen, NO<sub>2</sub>, NH<sub>2</sub>, NY<sup>2</sup>WY<sup>1</sup> or Het<sup>1</sup>.

More preferably R<sup>1</sup> when taken alone is OH, CN, I, Cl, NH<sub>2</sub>, NO<sub>2</sub>, optionally benzo-fused heteroaryl, NHSO<sub>2</sub>Y<sup>1</sup>, NHCOY<sup>1</sup> or NHCO<sub>2</sub>Y<sup>1</sup>.

- 30 Yet more preferably R<sup>1</sup> when taken alone is OH, CN, I, Cl, NH<sub>2</sub>, NO<sub>2</sub>, 1,2,3-triazolyl, 1,2,4-triazolyl, imidazol-2-yl, pyridin-2-yl, thien-2-yl, imidazol-4-yl, benzimidazol-2-yl, NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl), NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl substituted by methoxy, CONH<sub>2</sub>, OH,

CO<sub>2</sub>(C<sub>2-6</sub> alkyl), phthalimido, NH<sub>2</sub> or halogen), NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>NH(C<sub>1-6</sub> alkyl), NHSO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>, NHSO<sub>2</sub>Het<sub>1a</sub>, NHCO(C<sub>1-6</sub> alkyl) or NHCO<sub>2</sub>(C<sub>1-6</sub> alkyl).

Even more preferably R<sup>1</sup> is OH, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, NHSO<sub>2</sub>(n-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(i-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(n-C<sub>4</sub>H<sub>9</sub>), NHSO<sub>2</sub>NH(i-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(N-methylimidazol-4-yl),

5 NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OH, 1,2,4-triazolyl or imidazol-2-yl.

Most preferably R<sup>1</sup> is OH, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> or imidazol-2-yl.

Preferably R<sup>2</sup> when taken alone is H.

10 R<sup>1</sup> and R<sup>2</sup> when taken together with the carbon atoms to which they are attached are preferably an optionally benzo-fused 5- to 7-membered heteroaryl ring optionally substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl.

More preferably R<sup>1</sup> and R<sup>2</sup> when taken together with the carbon atoms to which they are attached are a 5-membered heteroaryl moiety optionally substituted by C<sub>1-4</sub> alkyl

15 or C<sub>1-4</sub> haloalkyl.

Yet more preferably R<sup>1</sup> and R<sup>2</sup> when taken together with the carbon atoms to which they are attached are an imidazole group optionally 2-substituted by CF<sub>3</sub>.

Preferably X is Cl.

20

Preferably n is 0.

Preferably q is 0.

25 Preferably R<sup>3</sup> is H, CN, C<sub>1-6</sub> alkyl (optionally substituted by one or more halogen, OH, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>2-6</sub> alkyloxycarbonyloxy, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> and/or NY<sup>2</sup>WY<sup>1</sup>).

More preferably R<sup>3</sup> is H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, i-C<sub>3</sub>H<sub>7</sub>, n-C<sub>3</sub>H<sub>7</sub> or CH<sub>2</sub>OCH<sub>3</sub>.

Most preferably R<sup>3</sup> is CH<sub>3</sub>.

30

Preferably R<sup>4</sup> is C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl or C<sub>3-10</sub> alkynyl each of which groups is linked to the N atom via a sp<sup>3</sup> carbon, each of which is optionally substituted by C<sub>3-8</sub>

cycloalkyl, aryl (optionally substituted by one or more methyl, ethyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, OH, =O, methoxy, OCF<sub>3</sub>), optionally benzo-fused heteroaryl (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, methoxy, OH, =O, OCF<sub>3</sub>), OH, aryloxy (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, OH, =O, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, methoxy, OCF<sub>3</sub>), CN, CF<sub>3</sub>, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, CONH(C<sub>3-8</sub> cycloalkyl), adamantyl, or (optionally benzo-fused) heteroaryloxy (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, OH, =O, methoxy, OCF<sub>3</sub>).

More preferably R<sup>4</sup> is n-hexyl, 3-phenylpropyl, 3-phenyloxypropyl, 3-cyclohexylpropyl, 5-methylhexyl, 2-phenyloxyethyl, (4-cyanomethyl)benzyl, 2-cyclohexyloxyethyl, 2-benzyloxyethyl, 3-cyclohexylprop-2-en-1-yl, 2-(cyclohexylcarbonyl)ethyl, 3-(2-methylphenyl)propyl, 3-phenylprop-2-en-1-yl, 2-(indol-3-yl)ethyl, 3-cyclohexyl-3-hydroxypropyl, (indan-2-yl)methyl, 3-(4-fluorophenyl)propyl, 3-(thien-2-yl)propyl, 3-(thien-3-yl)propyl, 3-(pyrid-2-yl)propyl, 3-(3-methylthien-2-yl)propyl, 3-(thien-2-yl)prop-2-en-1-yl, 3-(thien-3-yl)prop-2-en-1-yl, 3-(pyrid-2-yl)prop-2-en-1-yl, 3-(3-methylthien-2-yl)prop-2-en-1-yl, 3-(3-methylpyrid-2-yl)prop-2-en-1-yl or 3-(2-methoxyphenyl)propyl.

Yet more preferably R<sup>4</sup> is n-hexyl, 3-phenylpropyl, (4-cyanomethyl)benzyl, 2-benzyloxyethyl, 3-cyclohexylprop-2-en-1-yl, 2-(indol-3-yl)ethyl, 3-(2-methylphenyl)propyl, 3-(4-fluorophenyl)propyl, 3-(pyrid-2-yl)propyl, 3-phenylprop-2-en-1-yl, 3-cyclohexyl-3-hydroxypropyl, 3-(thien-2-yl)propyl, 3-(thien-3-yl)propyl, 3-(3-methylthien-2-yl)propyl, 3-(thien-2-yl)prop-2-en-1-yl, 3-(thien-3-yl)prop-2-en-1-yl, 3-(pyrid-2-yl)prop-2-en-1-yl, 3-(3-methylthien-2-yl)prop-2-en-1-yl, 3-(6-methylpyrid-2-yl)prop-2-en-1-yl or 3-(2-methoxyphenyl)propyl.

Preferably R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are each taken separately and are H.

A preferred group of substances are those in which the "Ar" ring, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, q and (X)<sub>n</sub> have the values as detailed in the Examples below.

A most preferred group of substances are those mentioned in the Examples, especially Examples 1, 5, 6, 10-13, 18, 20, 25-28, 32-34, 36, 38, 40, 42, 45, 47, 48, 57, 62, 67-

69, 76, 79, 80, 84, 88, 90, 92, 97, 99, 102, 113, 114, 118, 119, 122-124, 136, 139 and 143, and the salts and prodrugs thereof, even more especially those of Examples 1, 5, 10, 12, 13, 26, 28, 36, 40, 45, 47, 48, 62, 68, 69, 79, 80, 84, 88, 90, 97, 99, 102, 113, 118, 114, 119, 122-124, 136, 139 and 143 and the salts and prodrugs thereof. Yet  
5 more preferred are the compounds of Examples 1, 10, 13, 26, 28, 62, 68, 69, 79, 80, 84, 88, 90, 97, 102, 113, 114, 118, 119, 12, 123, 124, 136, 139, and 143 and the salts and prodrugs thereof. Most preferred are the compounds of Examples 1, 10, 26, 79, 97, 102, 118, 139 and 143 and the salts and prodrugs thereof.

10 The invention further provides synthetic methods for the production of compounds and salts of the invention, which are described below and in the Examples and Preparations. The skilled man will appreciate that the compounds of the invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example  
15 the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, VCH (1989 or later editions), "Advanced Organic Chemistry - Reactions, Mechanisms and Structure", J. March, Wiley-Interscience (3rd or later editions),  
20 "Organic Synthesis - The Disconnection Approach", S Warren (Wiley), (1982 or later editions), "Designing Organic Syntheses" S Warren (Wiley) (1983 or later editions), "Guidebook To Organic Synthesis" RK Mackie and DM Smith (Longman) (1982 or later editions), etc.,  
25 and the references therein as a guide.

It is to be understood that the synthetic transformation methods mentioned herein are exemplary only and they may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will  
30 exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound. For example, substituents may be added to and/or chemical transformations performed upon, different intermediates to those

mentioned hereinafter in conjunction with a particular reaction. This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

10

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1999), and references therein. Functional groups which may be desirable to protect include oxo, hydroxy, amino and carboxylic acid. Suitable protecting groups for oxo include acetals, ketals (e.g. ethylene ketals) and dithianes. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C<sub>1-6</sub> alkyl or benzyl esters.

20

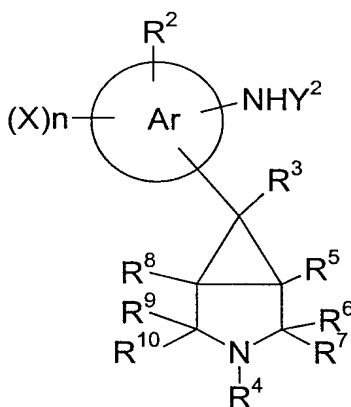
In the Methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (I).

25

The invention provides a process for the preparation of compounds of formula I as defined above, or a pharmaceutically or veterinarily acceptable derivative thereof, which comprises:

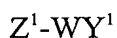
(a) for compounds of formula I in which *q* is 0 and R<sup>1</sup> represents NY<sup>2</sup>WY<sup>1</sup>, reacting a compound of formula II,

30



II

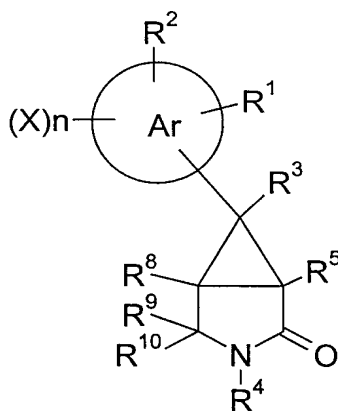
with a compound of formula III,



III

wherein  $Z^1$  is a suitable leaving group, such as halogen or  $Y^1SO_2O^-$  ;

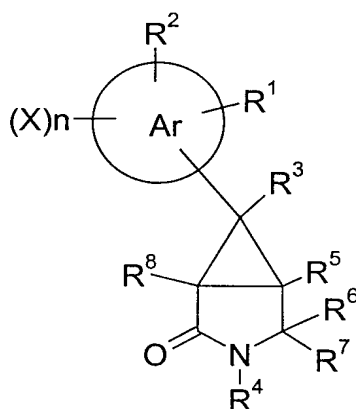
- 5 (b) for compounds of formula I in which  $q$  is 0 and  $R^6$  and  $R^7$  both represent H, reduction of a compound of formula IV,



IV

using a suitable reducing agent;

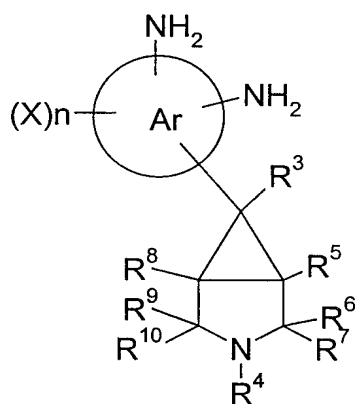
- (c) for compounds of formula I in which  $q$  is 0 and  $R^9$  and  $R^{10}$  both represent H,  
10 reduction of a compound of formula V,



V

using a suitable reducing agent;

(d) for compounds of formula I in which q is 0 and R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms and are taken together with the carbon atoms to which they are attached to represent Het<sup>1a</sup>, in which Het<sup>1a</sup> represents an imidazolo unit, reaction of a  
5 corresponding compound of formula VI,



VI

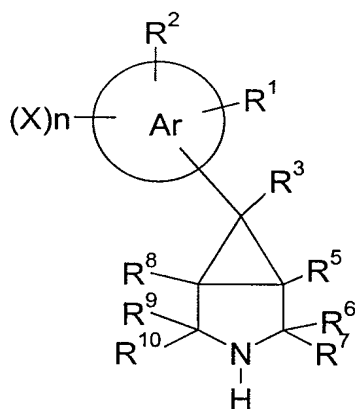
with a compound of formula VII,



VII

10 wherein R<sup>y</sup> represents H or any of the optional substituents on Het<sup>1a</sup> (as defined above), preferably H, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl;

(e) where q is 0, reacting a compound of formula VIII,



VIII

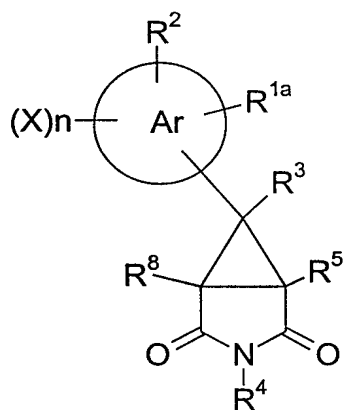
with a compound of formula IX,



IX

wherein Lg is a leaving group;

- 5 (f) for compounds of formula I in which q is 0 and  $R^6$ ,  $R^7$ ,  $R^9$  and  $R^{10}$  are all H, reduction of a compound of formula X,



X

with a suitable reducing agent;

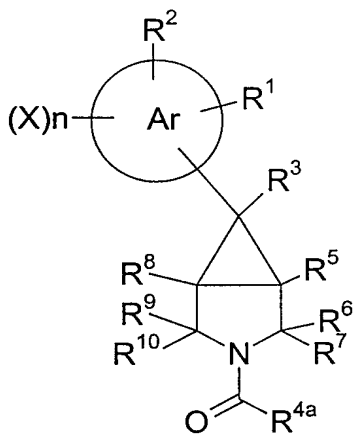


(g) for compounds of formula I in which q is 0 and  $R^1$  represents OH, reacting a compound of formula II in which  $Y^2$  is H, as defined above, with fluoroboric acid and isoamyl nitrite;

(h) for compounds of formula I in which q is 0 and  $R^1$  represents Cl, reacting a compound of formula II in which  $Y^2$  is H, as defined above, with sodium nitrite in the presence of dilute acid, followed by reaction with copper (I) chloride in the presence of concentrated acid;

(i) for compounds of formula I in which q is 1, reacting a compound of formula I where q is 0 with a suitable oxidising agent such as aqueous hydrogen peroxide; or

(j) for compounds of formula I where q is 0, by reduction of a corresponding compound of formula XXXI,



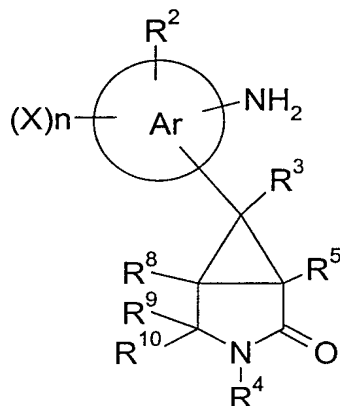
XXXI

where  $R^{4a}CH_2$  takes the same meaning as  $R^4$  as defined above,

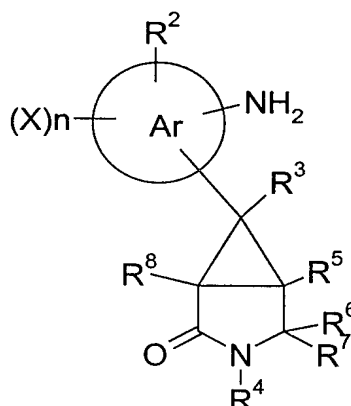
and where desired or necessary converting the resulting compound of formula I into a pharmaceutically or veterinarily acceptable derivative or vice versa.

In process (a), the reaction may be carried out at between  $0^\circ\text{C}$  and room temperature in the presence of a suitable base (e.g. pyridine) and an appropriate organic solvent (e.g. dichloromethane).

Compounds of formula II may be prepared by reduction of a corresponding compound of formula XI or formula XII,



XI

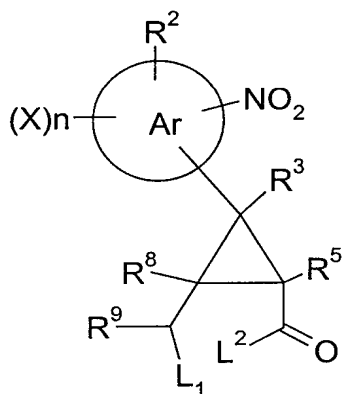


XII

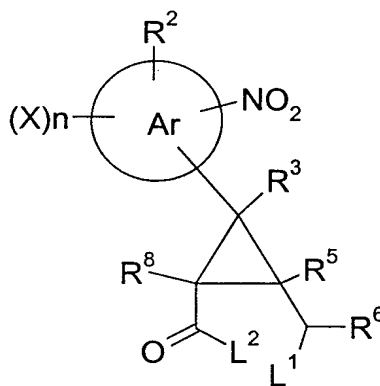
in the presence of a suitable reducing agent, such as lithium aluminium hydride. The reaction may be carried out at between room temperature and reflux temperature in the presence of a suitable solvent (e.g. tetrahydrofuran).

Compounds of formula XI and XII may be prepared by reduction of the corresponding -NO<sub>2</sub> compounds under conditions that are well known to those skilled in the art (e.g. using H<sub>2</sub>/Raney Ni or in the presence of CaCl<sub>2</sub> and iron powder, in the presence of a suitable solvent system (e.g. EtOH, EtOAc and/or water)). The skilled person will appreciate that, in preparing a compound of formula II, in which Y<sup>2</sup> is H, from such a corresponding -NO<sub>2</sub> compound, the two above-mentioned reduction steps may be performed in the same step or sequentially in any order.

The said corresponding -NO<sub>2</sub> compounds may be prepared by reaction of a compound of formula XII or formula XIV, as appropriate,

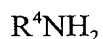


XIII



XIV

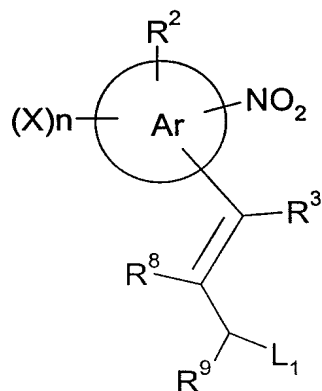
wherein  $L^1$  represents a suitable leaving group [such as halo (e.g. chloro or bromo)],  $L^2$  represents a suitable leaving group (such as  $C_{1-3}$  alkoxy) and  $R^3$  is as defined above, with a compound of formula XV,



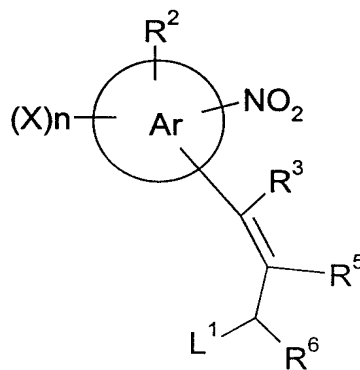
XV

The reaction may be carried out at between room temperature and reflux temperature in the presence of a suitable base (e.g.  $NaHCO_3$ ) and an appropriate organic solvent (e.g. dimethylformamide), or at a higher temperature (e.g. between 50 and 200°C, preferably between 100 and 160°C) in the presence of neat compound of formula XV.

Compounds of formula XIII and XIV may be prepared in accordance with standard techniques. For example, compounds of formula XIII and XIV may be prepared by reacting a corresponding compound of formula XVI or XVII,



XVI



XVII

with a compound of formula XVIII or XIX respectively,  
 $N_2CHR^5COL^2$

XVIII

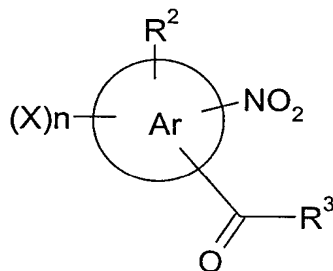


XIX

wherein  $\text{L}^2$  is as defined above. The reaction may be carried out at room temperature in the presence of a suitable catalyst [e.g.  $\text{Rh}_2(\text{OAc})_4$ ] and an appropriate non-protic organic solvent (e.g. dichloromethane).

5

Compounds of formula XVI and formula XVII are available or can be prepared using known techniques. Compounds of formula XVI and formula XVII may, for example, be prepared from corresponding compounds of formula XX,



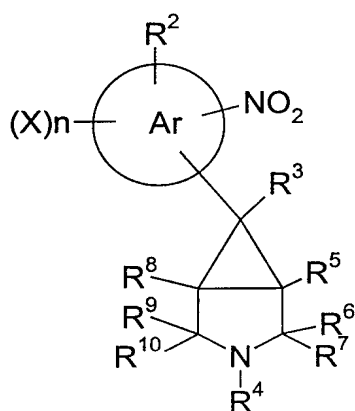
XX

- 10 for example by performing a Wittig reaction using an appropriate provider of the nucleophilic group  $\text{RO}_2\text{C}-\text{CR}^5\text{H}^-$  or  $\text{RO}_2\text{C}-\text{CR}^8\text{H}^-$  (wherein R represents lower (e.g.  $\text{C}_{1-3}$ ) alkyl), as appropriate, under conditions that are well known to those skilled in the art. The  $-\text{CO}_2\text{R}$  group of the resulting compound may be converted to an appropriate  $-\text{CH}_2\text{L}^1$  group using standard techniques (e.g. reduction of the ester to the primary
- 15 alcohol and conversion of the latter to an alkyl halide) under conditions that are well known to those skilled in the art.

- In processes (b) and (c), suitable reducing agents include lithium aluminium hydride. The reaction may be carried out at between room temperature and reflux temperature
- 20 in the presence of a suitable solvent (e.g. tetrahydrofuran).

Compounds of formula II may be prepared by reduction of the corresponding compound of formula XXX,

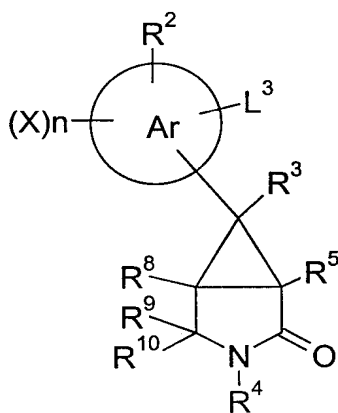
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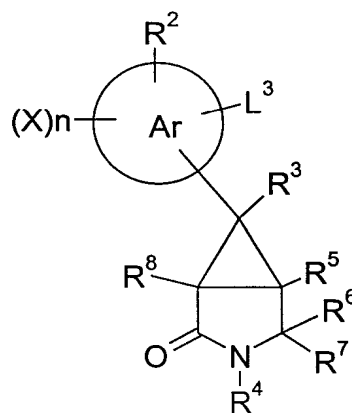
XXX

15 by analogy to the process steps mentioned above.

Compounds of formula IV and V may be prepared respectively from compounds of formula XXI and XXII,



XXI



XXII

20 wherein  $L^3$  represents a group that is capable of undergoing functional group transformations (e.g. cyano) using standard functional group substitution or conversion techniques.

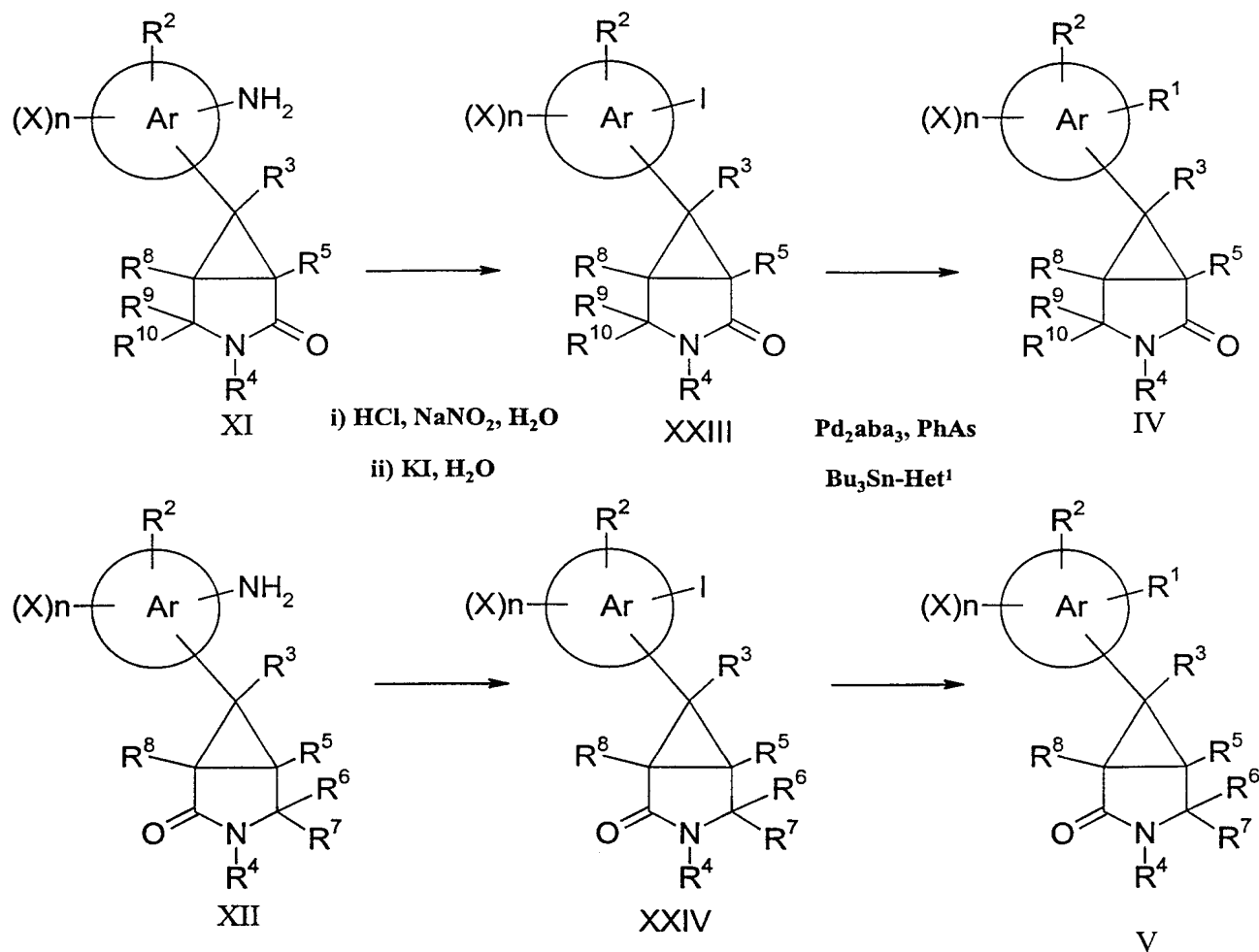
For example:

- (1) Compounds of formula IV and V in which R<sup>1</sup> represents 1,2,4-triazol-3-yl may be prepared by reaction of an appropriate compound of formula XXI or XXII in which L<sup>3</sup> represents -CN with HCl (gas) in the presence of an appropriate lower alkyl alcohol (e.g. ethanol), for example at between 0°C and room temperature, followed by reaction of the resultant intermediate with formic acid hydrazide (e.g. at reflux temperature, with or without the presence of a suitable organic solvent (e.g. methanol), followed by, if necessary, removing the solvent and heating the resultant residue to a high temperature (e.g. about 150°C)).
- 10 (2) Compounds of formula IV and V in which R<sup>1</sup> represents imidazol-2-yl may be prepared by reaction of an appropriate compound of formula XXI or XXII in which L<sup>3</sup> represents -CN with HCl (gas) in the presence of an appropriate lower alkyl alcohol (e.g. ethanol), for example at between 0°C and room temperature, followed by reaction of the resultant intermediate with aminoacetaldehyde dialkylacetal (e.g. 15 dimethylacetal) (e.g. at or around reflux temperature in the presence of an appropriate solvent, such as methanol).
- (3) Compounds of formula IV and V in which R<sup>1</sup> represents 1,2,3-triazol-5-yl may be prepared by reaction of an appropriate compound of formula XXI or XXII in which L<sup>3</sup> represents -CN with diazomethane, or a protected (e.g. trialkylsilyl) derivative 20 thereof, for example at between 0°C and room temperature in the presence of a suitable base (e.g. n-BuLi) and, optionally, an appropriate organic solvent (e.g. THF), followed by removal of the protecting group as necessary.
- (4) Compounds of formula IV and V in which R<sup>1</sup> represents benzimidazol-2-yl may be prepared by reaction of an appropriate compound of formula XXI or XXII in 25 which L<sup>3</sup> represents C=NH(OEt) with 1,2-diaminobenzene. The reaction may be carried out in a solvent such as methanol, at an elevated temperature (such as the reflux temperature of the solvent). **Preparations 81, etc. provide further details.**

Compounds of formula IV and V in which R<sup>1</sup> represents Het<sup>1</sup> may also be prepared 30 from compounds of formula XI and XII respectively according to the following scheme:

wherein Het<sup>1</sup> is defined above. Further details may be found in Preparations 67, 68, etc. below.

Compounds of formula XXI and XXII may be prepared in analogous fashion to methods described herein, for example those described hereinbefore for preparation of compounds of formula II.



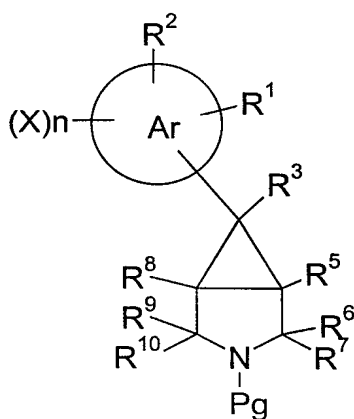
Other compounds of formula (IV) and (V) may be prepared by analogy with methods described herein (e.g. by analogy with methods described hereinbefore for preparation of compounds of formula XI and XII (and especially the corresponding -NO<sub>2</sub> compound)).

In process (d), the reaction may be carried out by heating under reflux, with or without the presence of an appropriate organic solvent.

Compounds of formula VI may be prepared using known techniques. For example, compounds of formula VI may be prepared by nitration (at the 4-position) of a corresponding 3-aminobenzene compound (a compound of formula II), which latter compound may be activated by converting the 3-amino group to a 3-amido group, followed by hydrolysis of the amide and reduction of the 4-nitrobenzene compound. All of these reactions may be performed using techniques that are familiar to the skilled person, and are **illustrated in Preparations 45-48, etc. below.**

In process (e), suitable leaving groups that Lg may represent include halogen, such as bromine, or a sulphonate group such as tosylate. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example dimethylformamide), at an elevated temperature (for example 50°C), in the presence of a base (for example sodium hydrogen carbonate). A catalyst such as sodium iodide may optionally be added.

Compounds of formula VIII may be prepared from compounds of formula XXV,



XXV

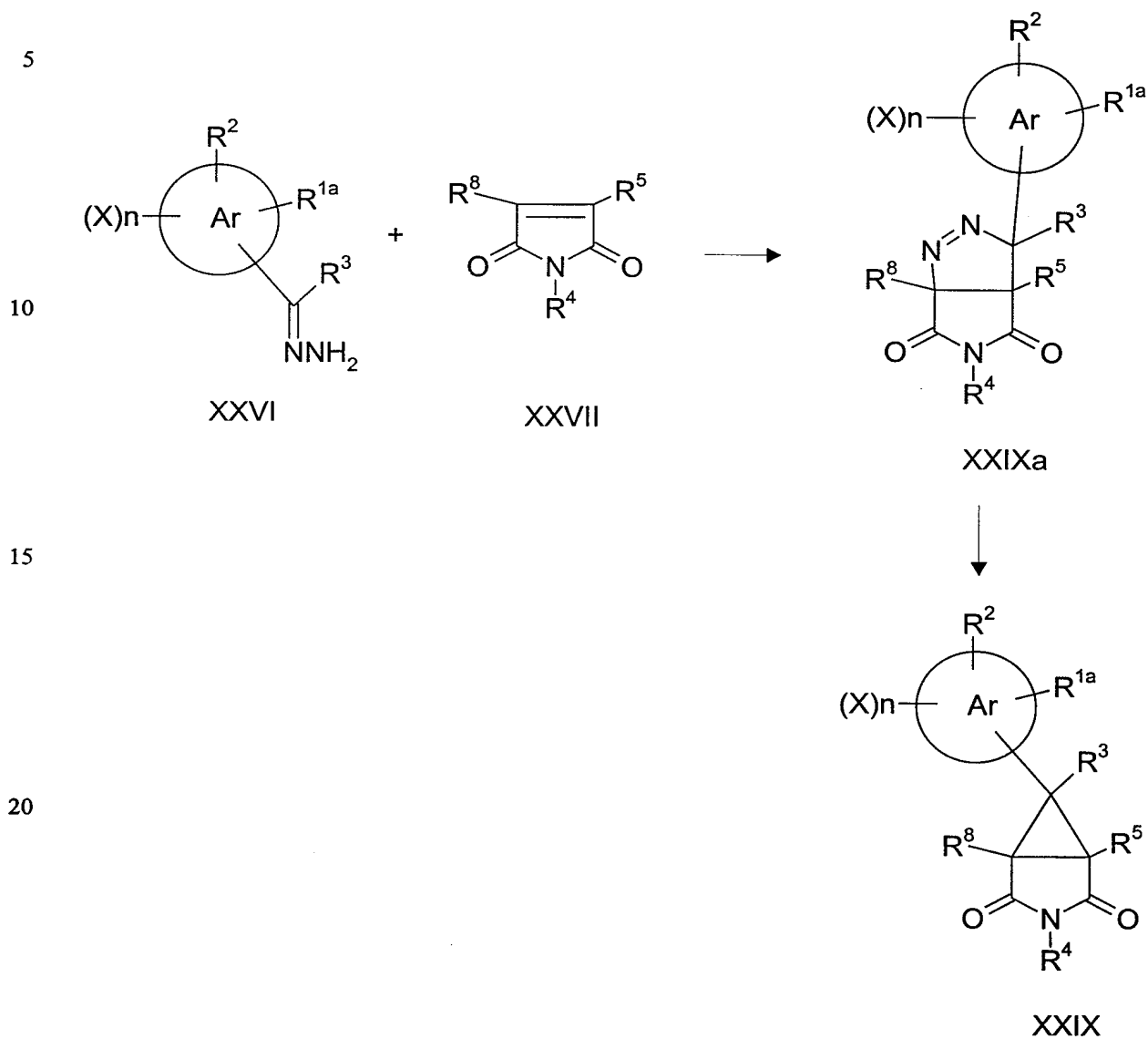
wherein Pg represents a suitable protecting group. Suitable protecting groups include allyl, which may be removed using a palladium (0) catalyst and N,N-dimethylbarbituric acid (see Preparation 53, etc. below). Compounds of formula



XXV may be prepared using analogous methods to those described herein for the preparation of compounds of formula I.

5 In process (f), suitable reducing agents include lithium aluminium hydride. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example tetrahydrofuran), at an elevated temperature (for example the reflux temperature of the solvent).

10 Compounds of formula X may be prepared by reacting a compound of formula XXVI with a compound of formula XXVII in the presence of an oxidizing agent. Suitable oxidizing agents include manganese dioxide. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example dioxan), at an elevated temperature such as the reflux temperature of the solvent (for example see Preparation 77, etc. below). The intermediate compounds XXIXa are isolatable using suitable  
15 conditions (e.g. see Preparation 58).



Compounds of formula XXVI may be prepared from compounds of formula XXVIII, by reaction of the corresponding ketone with hydrazine monohydrate using known techniques (and as described in Preparation 76, etc. below).

Process (f) is particularly useful when Ar represents an optionally benzo-fused 5- or 6-membered heteroaryl ring. A similar methodology may be used to obtain compounds of formula II: the precursor nitro compound may be prepared from a compound of formula XX, as defined above, using the steps described above (see for example Preparations 57-61, etc.).

In process (g), the reaction may be carried out in a solvent that does not adversely affect the reaction (for example ethanol), first below room temperature and then at an elevated temperature (Examples 79, etc. provide further details).

In process (h), suitable acids include dilute aqueous hydrochloric acid and concentrated hydrochloric acid, respectively. The reaction may be carried out at or around room temperature, finishing at an elevated temperature (for example 90°C). Examples 51 provide further details.

In process (j), the compound of formula XXXI may be prepared by acylation of the compound of formula VIII as defined above, with an acylating agent of the formula  $R^{4a}CO-L_g$ , where  $L_g$  is a suitable leaving group as defined above with respect to (e), and includes halogen, (alkyl, haloalkyl or aryl)sulphonate,  $OCOR^{4a}$  (i.e. an acid anhydride) and the like, well known to those practising in the art. See for example the conditions used for Preparation 47.

It will be apparent to those skilled in the art that compounds of formula I may be converted to other compounds of formula I using known techniques. For example, compounds of formula I in which  $Y^1$  represents alkoxy carbonyl may be converted to compounds in which  $Y^1$  represents alkyl substituted by OH, by reduction using  $LiAlH_4$  (Example 57 provides further details). Similarly, intermediate compounds may be interconverted using known techniques (see for example Preparation 85).

The intermediate compounds such as those of formulae III, XV, XVIII, XIX, XX, VII, IX, XXVI, XXVII and XXVIII, and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the

processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

- 5 The invention further provides the intermediate compounds of formulae II, IV, V, VI, VIII, X, X<sup>a</sup>, XI, XII, XIII, XIV, XXI, XXII, XXIII, XXIV, XXV, XXIX, XXIX<sub>a</sub>, XXX, XXXI as defined above.
- 10 Where desired or necessary, the compound of formula (I) can be converted into a pharmaceutically acceptable salt thereof, conveniently by mixing together solutions of a compound of formula (I) and the desired acid or base, as appropriate. The salt may be precipitated from solution and collected by filtration, or may be collected by other means such as by evaporation of the solvent. Both types of salt may also be formed or
- 15 interconverted using ion-exchange resin techniques.

The compounds of the invention may be purified by conventional methods, for example separation of diastereomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric

20 mixture of a compound of formula (I) or a salt thereof. An individual enantiomer of a compound of formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereomeric salts formed by reaction of the corresponding racemate with a suitably optically active

25 base or acid.

The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals including humans. They are therefore indicated as pharmaceuticals and, in particular, for use as animal medicaments.

30

According to a further aspect of the invention there is provided the compounds of the invention for use as medicaments, such as pharmaceuticals and animal medicaments.

By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

In particular, the substances of the invention have been found to be useful in the treatment of diseases and conditions modulated *via* opiate receptors, such as irritable bowel syndrome; constipation; nausea; vomiting; pruritus; eating disorders; opiate overdoses; depression; smoking and alcohol addiction; sexual dysfunction; shock; stroke; spinal damage and/or head trauma; and conditions characterised by having pruritis as a symptom.

Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a disease modulated *via* an opiate receptor. There is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of as irritable bowel syndrome; constipation; nausea; vomiting; pruritus; eating disorders; opiate overdoses; depression; smoking and alcohol addiction; sexual dysfunction; shock; stroke; spinal damage and/or head trauma; and conditions characterised by having pruritis as a symptom.

The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and conditions which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

Thus, the invention provides a method of treating or preventing a disease modulated *via* an opiate receptor. There is further provided a method of treating irritable bowel syndrome; constipation; nausea; vomiting; pruritus; eating disorders; opiate overdoses; depression; smoking and alcohol addiction; sexual dysfunction; shock; stroke; spinal damage and/or head trauma; or a medical condition characterised by pruritus as a symptom in an animal (e.g. a mammal), which comprises administering a

therapeutically effective amount of a compound of the invention to an animal in need of such treatment.

The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (eg subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient.

5 The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For veterinary use, the compounds of the invention are of particular value for treating  
10 pruritus in domestic animals such as cats and dogs and in horses.

As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

15 For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet, capsule and ointment preparations which are formulated in accordance with standard pharmaceutical  
20 practice.

Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of  
25 illustration and should not be construed as limiting) include antiparasitics, eg fipronil, lufenuron, imidacloprid, avermectins (eg abamectin, ivermectin, doramectin), milbemycins, organophosphates, pyrethroids; antihistamines, eg chlorpheniramine, trimeprazine, diphenhydramine, doxylamine; antifungals, eg fluconazole, ketoconazole, itraconazole, griseofulvin, amphotericin B; antibacterials, eg  
30 enrofloxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammatories eg prednisolone, betamethasone, dexamethasone, carprofen, ketoprofen; dietary supplements, eg gamma-linoleic acid; and emollients. Therefore, the invention

further provides a product containing a compound of the invention and one or more selected compounds from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of diseases modulated *via* opiate receptors

- 5 The skilled person will also appreciate that compounds of the invention may be taken as a single dose or on an "as required" basis (i.e. as needed or desired).

Thus, according to a further aspect of the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention in  
10 admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be more efficacious than, be less toxic than,  
15 have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

The biological activities of the compounds of the present invention were determined  
20 by the following test method.

### **Biological Test**

Compounds of the present invention have been found to display activity in three  
25 opioid receptor binding assays selective for the mu, kappa and delta opioid receptors in dog brain. The assays were conducted by the following procedure.

Laboratory bred beagles were used as a source of dog brain tissue. Animals were euthanased, their brains removed and the cerebellum discarded. The remaining brain  
30 tissue was sectioned into small pieces approximately 3 g in weight and homogenised in 50mM Tris pH 7.4 buffer at 4°C using a Kinematica Polytron tissue homogeniser. The resulting homogenate was centrifuged at 48,400 x g for 10 minutes and the



supernatant discarded. The pellet was resuspended in Tris buffer and incubated at 37°C for 10 minutes. Centrifugation, resuspension and incubation steps were repeated twice more, and the final pellet was resuspended in Tris buffer and stored at -80°C. Membrane material prepared in this manner could be stored for up to four weeks prior to use.

For mu, kappa and delta assays, increasing concentrations of experimental compound ( $5 \times 10^{-12}$  to  $10^{-5}$ M), Tris buffer and  $^3\text{H}$  ligand, ( $\mu$  = [D-Ala<sup>2</sup>,N-Me-Phe<sup>4</sup>,Gly-ol<sup>5</sup>]-Enkephalin, DAMGO; kappa = U-69,593; delta = Enkephalin, [D-pen<sup>2,5</sup>] DPDPE), were combined in polystyrene tubes. The reaction was initiated by the addition of tissue, and the mixture was incubated at room temperature for 90 minutes. The reaction was terminated by rapid filtration using a Brandel Cell Harvester™ through Betaplate™ GF/A glass fibre filters pre-soaked in 50 mM Tris pH 7.4, 0.1% polyethylenimine buffer. The filters were then washed three times with 0.5 ml ice-cold Tris pH 7.4 buffer. For mu and delta assays, washed filters were placed in bags and Starscint™ scintillant added, for the kappa assay Meltilex™ B/HS solid scintillant was used. Bags containing the filters and scintillant were heat sealed and counted by a Betaplate™ 1204 beta counter.

Duplicate samples were run for each experimental compound and the data generated was analysed using IC<sub>50</sub> analysis software in Graphpad Prism. Ki values were calculated using Graphpad Prism according to the following formula:

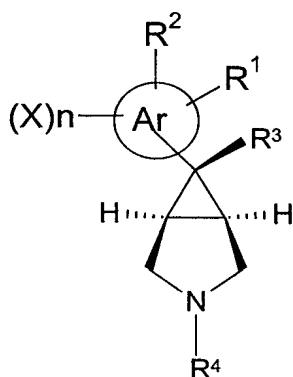
$$K_i = IC_{50} / 1 + [^3\text{H ligand}] / K_D$$

where IC<sub>50</sub> is the concentration at which 50% of the  $^3\text{H}$  ligand is displaced by the test compound and K<sub>D</sub> is the dissociation constant for the  $^3\text{H}$  ligand at the receptor site.

### Biological Activity

The  $K_i$  values of certain compounds of the present invention in the opioid receptor binding assays were determined, and the compounds of Examples 1, 6, 8, 14-16, 19 and 21-24 were found to have  $K_i$  values of 4000 nM or less for the  $\mu$  receptor.

- 5 It is believed that the methods used in the following Examples produce compounds having the relative stereochemistry shown below, and such compounds are preferred:



wherein  $R^{1-4}$  and  $(X)_n$  are as defined above.

The invention is illustrated by the following Examples and Preparations in which the following abbreviations may be used:

APCI = atmospheric pressure chemical ionization

5 DMF = dimethylformamide

DMSO = dimethylsulphoxide

d (in relation to time) = day

d (in relation to NMR) = doublet

ES (in relation to MS) = electrospray

10 EtOAc = ethyl acetate

EtOH = ethanol

h = hour

MeOH = methanol

min = minute

15 MS = mass spectrum

n-BuOH = n-butanol

ODS = octadecylsilyl

THF = tetrahydrofuran

TSP = thermospray

20

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectral data relate to <sup>1</sup>H and were obtained using a Varian Unity 300 or 400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. Mass spectral (MS) data were obtained on a  
25 Fisons Instruments Trio 1000, or a Fisons Instruments Trio 1000 APCI, or a Finnigan Navigator MS, or a Micromass Platform LC spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. Room temperature means 20 to 25°C. The mass spectrometer which is used as a detector on the analytical HPLC-MS system is a Micromass VG Platform II, running on Masslynx/Openlynx software. The  
30 system can run positive and negative ion with either Electrospray or APCI probes and is calibrated to 1972 Daltons, it collects full Diode array data from 190nm to 600nm.

HPLC means high performance liquid chromatography. HPLC conditions used were:

Condition 1: Rainin Dynamax™ column, 8μ ODS, 24 x 300 mm, column temperature 40°C, flow rate 45 ml/min, eluting with methanol : water (70 : 30), UV detection of product at 246 nm.

Condition 2: Rainin Dynamax™ column, 5μ ODS, 21.6 x 250 mm, column temperature 40°C, flow rate 5 ml/min, eluting with acetonitrile : water (50 : 50), UV detection of product at 246 nm.

Condition 3: Rainin Dynamax™ column, 8μ ODS, 41 x 250 mm, column temperature 40°C, flow rate 45 ml/min, eluting with acetonitrile : 0.1M aqueous ammonium acetate buffer (50 : 50), UV detection of product at 235 nm.

Condition 4: Phenomenex Magellan™ column, 5μ C<sub>18</sub> silica, 21.2 x 150 mm, column temperature 40°C, flow rate 20 ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous ammonium acetate buffer (30 : 70 to 95 : 5 over 10 min), UV detection of product at 220 nm.

Condition 5: Phenomenex Magellan™ column, 5μ ODS, 21.2 x 150 mm, column temperature 40°C, flow rate 20 ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous ammonium acetate buffer (5 : 95 to 95 : 5 over 20 min), UV detection of product at 215 nm.

Condition 6: Phenomenex Magellan™ column, 5μ C<sub>18</sub> silica, 4.6 x 150 mm, column temperature 40°C, flow rate 1 ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous heptanesulphonic acid (10 : 90 to 90 : 10 over 30 min), UV detection of product at 220 nm.

Condition 7: Phenomenex Magellan™ column, 5μ C<sub>18</sub> silica, 21.2 x 150 mm, column temperature 40°C, flow rate 20 ml/min, eluting with a gradient of acetonitrile : 0.05M aqueous ammonium acetate buffer (50 : 50 for 15 min then 50 : 50 to 90 : 10 over 5 min), UV detection of product at 220 nm.

Condition 8: Phenomenex Magellan™ column, 5μ C<sub>18</sub> silica, 21.2 x 150 mm, column temperature 40°C, flow rate 20 ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous ammonium acetate buffer (15 : 85 to 85 : 15), UV detection of product at 220 nm.

Condition 9: Phenomenex Magellan™ column, 5μ ODS, 10 x 150 mm, column temperature 40°C, flow rate 5ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous

ammonium acetate buffer (5 : 95 to 30 : 70 over 5 min then 30 : 70 for a further 20 min), UV detection of product at 225nm.

Condition 10: Phenomenex Magellan™ column, 5μ C<sub>18</sub> silica, 21.2 x 150mm, column temperature 40°C, flow rate 20 ml/min, eluting with a gradient of acetonitrile : 0.1M aqueous ammonium acetate (5 : 95 to 40 : 60 over 5 min then 40 : 60 for a further 25 min), UV detection of product at 210 nm.

Condition 11: Phenomenex Magellan™ column, 5μ ODS, 10 x 150mm, column temperature 40°C, flow rate 5 ml/min, eluting with a gradient of acetonitrile : water (5 : 95 to 55 : 45 over 5 min), UV detection of product at 210 nm.

10

The free base form of the azabicycles could be obtained from the hydrochloride or acetate salts, for example, in the following way. The salt (0.3 mmol) was dissolved in dichloromethane (20 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (20 ml). The basic mixture was separated and the aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the free base.

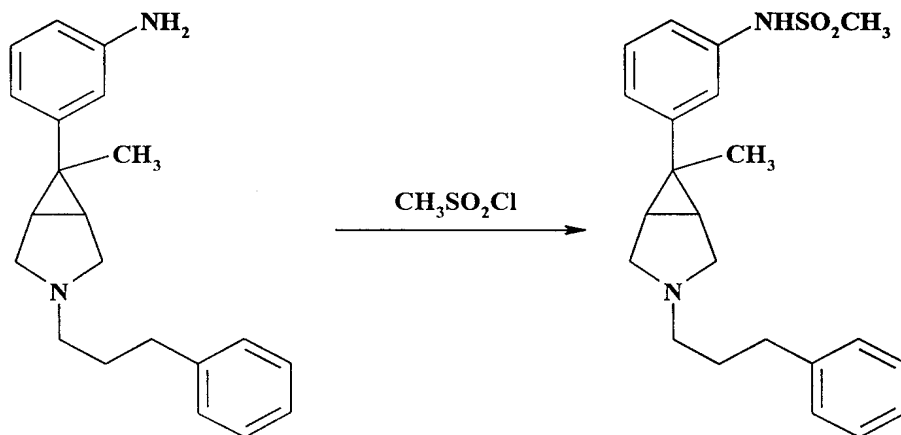
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SPE cartridge refers to a solid phase extraction cartridge. These can be commercially obtained from Varian (Mega Bond Elut®) or Isolute™.

20

#### Example 1

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]  
phenyl}}methanesulfonamide



25

To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 28 mg, 0.09 mmol) in dichloromethane (2 ml), at 0°C under nitrogen was added pyridine (20 µl, 0.24 mmol) and then methanesulfonylchloride (25 µl, 37 mg, 0.32 mmol) over 5 minutes. The mixture was allowed to warm to room temperature and was then stirred for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (5 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil (18 mg, 52%).

10 NMR (CDCl<sub>3</sub>) δ: 1.56 (s, 3H), 1.77 (m, 4H), 2.48 (t, 2H), 2.66 (t, 2H), 2.80 (d, 2H), 3.01 (s, 3H), 3.05 (d, 2H), 7.01 (d, 1H), 7.07 (m, 2H), 7.14 - 7.3 (m, 6H).

MS (thermospray) : M/Z [MH<sup>+</sup>] 385.4; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>SO<sub>2</sub> + H requires 385.2

#### Example 2

15 N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide acetate salt

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Example 1, 260 mg, 0.67 mmol) was purified further by preparative HPLC (condition 3). Combination and evaporation of pure fractions gave the title compound as a white solid (87 mg)

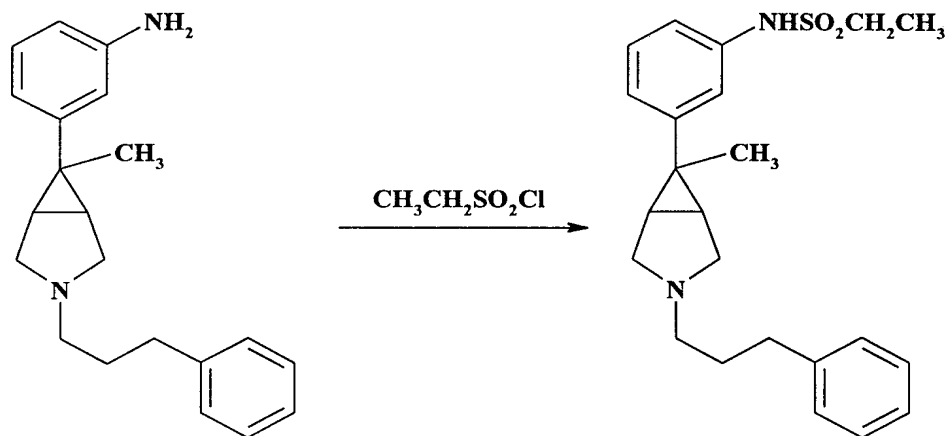
mp 116-117°C

20 NMR (CD<sub>3</sub>OD) δ: 1.45 (s, 3H), 1.93 (m, 5H), 2.09 (s, 2H), 2.67 (t, 2H), 2.86 (t, 2H), 2.93 (s, 3H), 3.05 (d, 2H), 3.46 (d, 2H), 7.04 (m, 2H), 7.10 - 7.33 (m, 7H)

25

#### Example 3

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-1-ethanesulfonamide



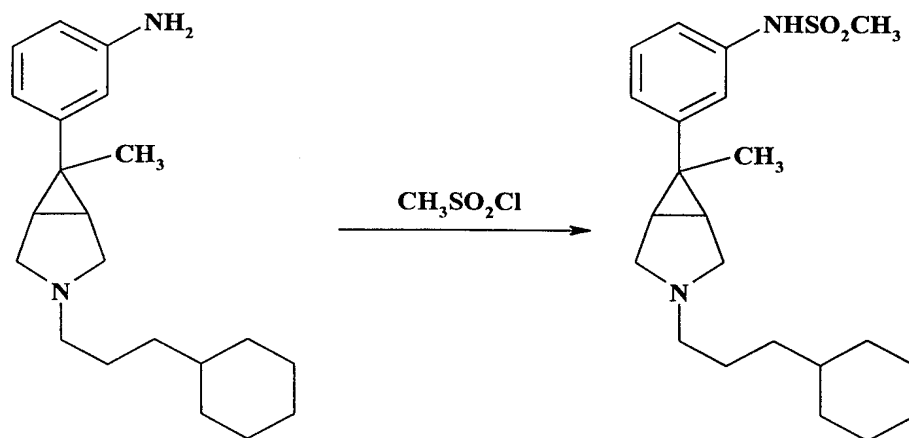
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 110 mg, 0.36 mmol) in dichloromethane (4 ml), at 0°C under nitrogen was added pyridine (56 µl, 0.72 mmol) then dropwise over 5 minutes ethanesulfonylchloride (67 µl, 92 mg, 0.72 mmol). The mixture was allowed to warm to room temperature and was stirred for 16 hours. Further pyridine (56 µl, 0.72 mmol) and ethanesulfonylchloride (67 µl, 92 mg, 0.72 mmol) were added and the mixture was stirred for 2 hours. The crude mixture was purified by silica (40 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil (48 mg, 34%).

NMR (CDCl<sub>3</sub>) δ: 1.39 (t, 3H), 1.57 (s, 3H), 1.76 (m, 4H), 2.48 (t, 2H), 2.66 (t, 2H), 2.80 (d, 2H), 3.04 (d, 2H), 3.12 (q, 3H), 6.97-7.11 (m, 3H), 7.11-7.33 (m, 6H).

MS (thermospray) : M/Z [MH<sup>+</sup>] 399.2; C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>SO<sub>2</sub> + H requires 399.2

#### Example 4

N-{3-[3-(3-Cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]-phenyl}methanesulfonamide



To a solution of 3-[3-(3-cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 10, 25 mg, 0.08 mmol) in dichloromethane (2 ml) at 0°C under nitrogen was added pyridine (20  $\mu$ l, 0.24 mmol) then dropwise over 5 minutes methanesulfonylchloride (25  $\mu$ l, 37 mg, 0.32 mmol). The mixture was allowed to warm to room temperature and was stirred for 90 minutes. Further methanesulfonylchloride (10  $\mu$ l, 15 mg, 0.13 mmol) was added and the mixture was stirred for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by silica (5 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (18 mg, 58%).

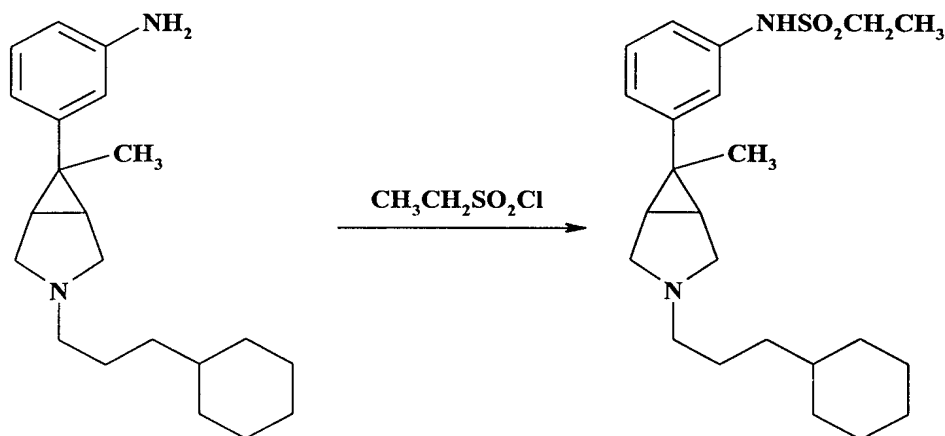
NMR (CDCl<sub>3</sub>)  $\delta$ : 0.90 (m, 2H), 1.06 -1.31 (m, 6H), 1.43 (m, 2H), 1.51 (s, 3H), 1.60-1.76 (m, 7H), 2.43 (t, 2H), 2.81 (d, 2H), 2.99 (d, 2H), 3.01 (s, 3H), 6.98-7.10 (m, 3H), 7.24 (m, 1H).

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 391.5.; C<sub>22</sub>H<sub>34</sub>N<sub>2</sub>SO<sub>2</sub> + H requires 391.2

#### Example 5

N-{3-[3-(3-Cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-1-ethanesulfonamide





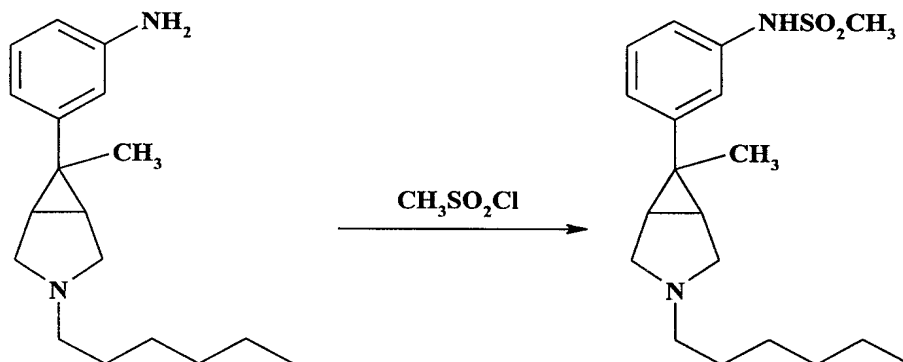
To a solution of 3-[3-(3-cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 10, 25 mg, 0.08 mmol) in dichloromethane (2 ml) at 0°C under nitrogen was added pyridine (20  $\mu\text{l}$ , 0.24 mmol) then dropwise over 5 minutes ethanesulfonylchloride (25  $\mu\text{l}$ , 34 mg, 0.26 mmol). The mixture was allowed to warm to room temperature and was stirred for 1.5 h. Further ethanesulfonylchloride (25  $\mu\text{l}$ , 34 mg, 0.26 mmol) was added and the mixture was stirred for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (5 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (21 mg, 65%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (m, 2H), 1.06 -1.31 (m, 6H), 1.37 (t, 3H), 1.44 (m, 2H), 1.51 (s, 3H), 1.60-1.76 (m, 7H), 2.43 (t, 2H), 2.83 (d, 2H), 2.98 (d, 2H), 3.13 (q, 2H), 6.98-7.10 (m, 3H), 7.24 (t, 1H)

MS (thermospray):  $m/z$  [ $\text{MH}^+$ ] 405.6.;  $\text{C}_{23}\text{H}_{36}\text{N}_2\text{SO}_2 + \text{H}$  requires 405.3

### Example 6

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



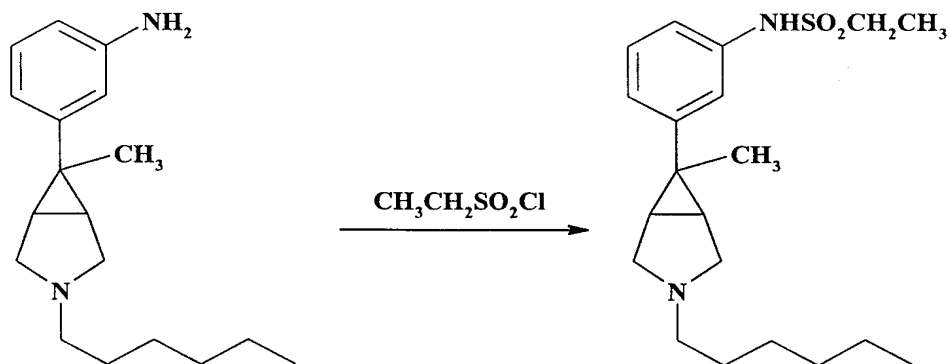
To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 200 mg, 0.735 mmol) in dichloromethane (5 ml) at room temperature was added pyridine (0.15 ml, 1.84 mmol) then dropwise over 5 minutes methanesulfonylchloride (0.11 ml, 158 mg, 1.38 mmol). The mixture was stirred for 48 h, concentrated *in vacuo* and the residue was purified by silica (10 g) column chromatography eluting with 90:10:1 ethyl acetate:methanol:ammonia solution (0.880), then in 80:20:1 ethyl acetate:methanol:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (212 mg, 82%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.90 (t, 3H), 1.28 (m, 6H), 1.47 (s, 3H), 1.54 (m, 2H), 1.90 (s, 2H), 2.60 (t, 2H), 2.97 (d, 2H), 3.00 (s, 3H), 3.15 (m, 2H), 7.02 (d, 1H), 7.07-7.15 (m, 2H), 7.22 (m, 1H)

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 351.1; C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>SO<sub>2</sub> + H requires 351.2

### Example 7

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide



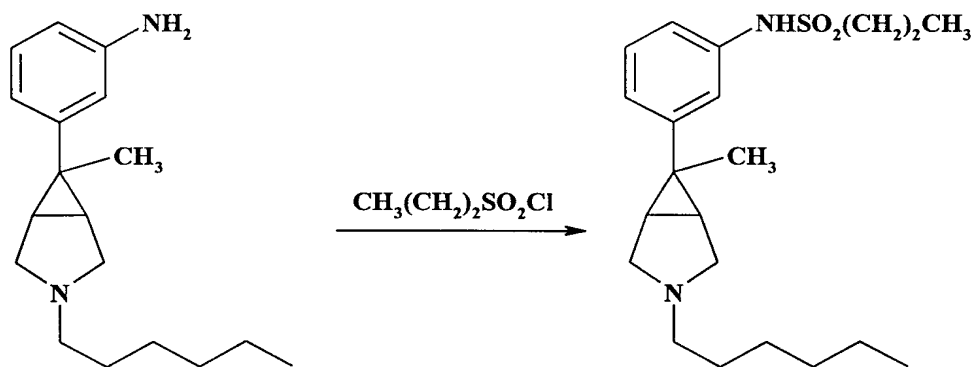
To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 200 mg, 0.735 mmol) in dichloromethane (5 ml) at room temperature was added pyridine (0.15 ml, 1.84 mmol) then dropwise over 5 minutes ethanesulfonylchloride (0.131 ml, 177 mg, 1.38 mmol). The mixture was stirred for 48 hours, concentrated *in vacuo* and the residue was purified by silica (10 g) column chromatography eluting with ethyl acetate then 90:10:1 ethyl acetate:methanol:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (140 mg, 52%).

10 NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (t, 3H), 1.28 (m, 6H), 1.34 (t, 3H), 1.47 (s, 3H), 1.55 (m, 2H), 1.90 (s, 2H), 2.63 (m, 2H), 2.97 (m, 2H), 3.11 (q, 2H), 3.20 (m, 2H), 7.02 (d, 1H), 7.04-7.15 (m, 2H), 7.21 (m, 1H)

MS (thermospray):  $m/z$  [ $\text{MH}^+$ ] 365.3;  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{SO}_2 + \text{H}$  requires 365.2

15 Example 8

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-propanesulfonamide



20 To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 200 mg, 0.735 mmol), in dichloromethane (5 ml) at room temperature was added pyridine (0.15 ml, 1.84 mmol) then dropwise over 5 minutes propanesulfonylchloride (0.16 ml, 202 mg, 1.42 mmol). The mixture was stirred for 48 hours, concentrated *in vacuo* and the residue was purified by silica (10 g) column chromatography  
25 eluting with ethyl acetate then 90:10:1 ethyl acetate:methanol:ammonia solution (0.880).

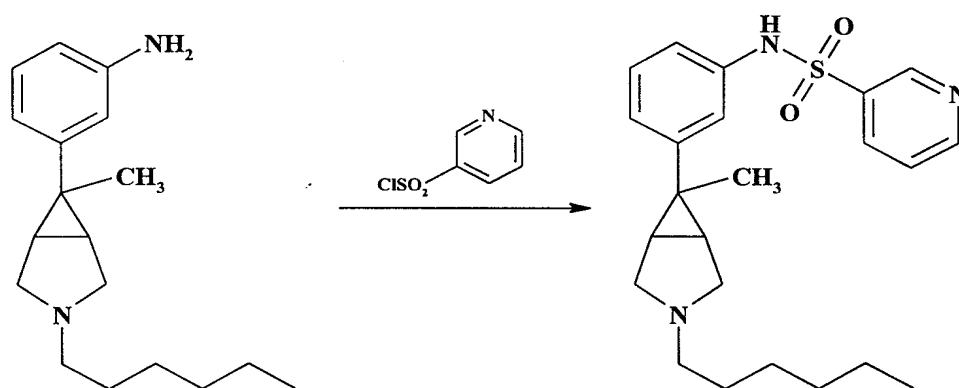
Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (40 mg, 14%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.90 (t, 3H), 1.02 (t, 3H), 1.30 (m, 6H), 1.46 (m, 2H), 1.50 (s, 3H), 1.77 (s, 2H), 1.87 (m, 2H), 2.47 (t, 2H), 2.87 (m, 2H), 2.93-3.07 (m, 4H), 6.97-7.09 (m, 3H), 7.22 (m, 1H)

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 379.2; C<sub>21</sub>H<sub>34</sub>N<sub>2</sub>SO<sub>2</sub> + H requires 379.2

### Example 9

#### N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-3-pyridinesulfonamide



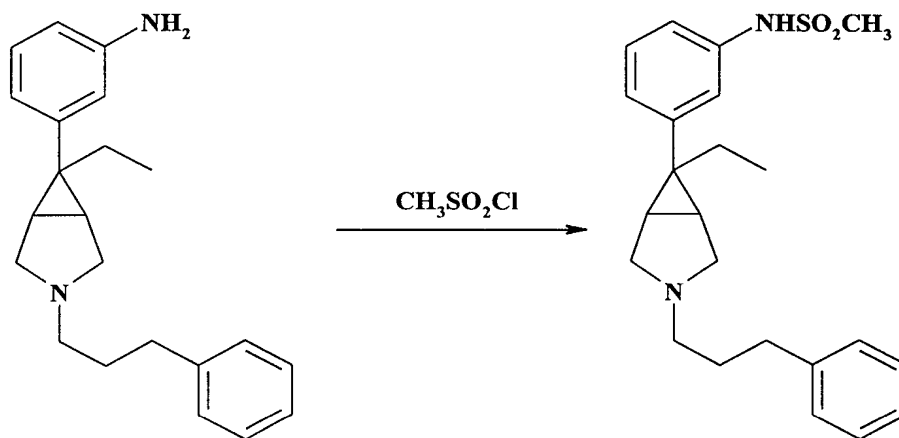
To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 220 mg, 0.809 mmol) in dichloromethane (5 ml) at room temperature was added pyridine (0.196 ml, 2.42 mmol) then dropwise over 5 minutes 3-pyridinesulfonylchloride (198 mg, 1.21 mmol). The mixture was stirred for 48 hours, concentrated *in vacuo* and the residue was purified by silica (10 g) column chromatography eluting with ethyl acetate then 90:10:1 ethyl acetate:methanol:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale orange oil (200 mg, 60%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.89 (t, 3H), 1.30 (m, 6H), 1.40 (s, 3H), 1.52 (m, 2H), 1.77 (s, 2H), 2.58 (t, 2H), 2.91 (d, 2H), 3.11 (m, 2H), 6.91-7.04 (m, 3H), 7.13 (t, 1H), 7.35 (m, 1H), 8.06 (d, 1H), 8.73 (d, 1H), 8.94 (s, 1H)

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 414.2; C<sub>23</sub>H<sub>31</sub>N<sub>3</sub>SO<sub>2</sub> + H requires 414.2

### Example 10

N-{3-[6-ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide acetate salt



5

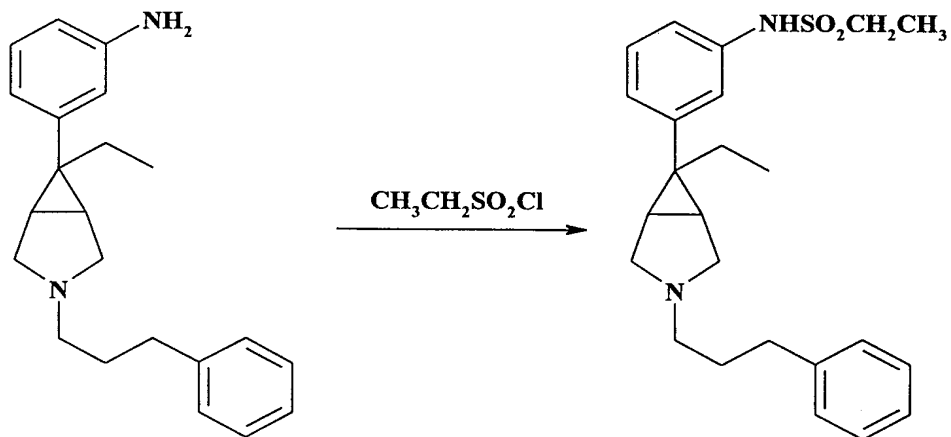
To a solution of 3-[6-ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 18, 500 mg, 1.56 mmol) in dichloromethane (20 ml), at 0°C under nitrogen was added pyridine (0.20 ml, 2.6 mmol) then dropwise over 5 minutes methanesulfonylchloride (0.20 ml, 300 mg, 2.6 mmol). The mixture was allowed to warm to room temperature and was stirred for 18 h. The mixture was concentrated *in vacuo* and the residue was purified by silica (25 g) column chromatography eluting with 70:30:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil. This was further purified by preparative HPLC (condition 3). Combination and evaporation of pure fractions gave the title compound as a white solid (140 mg, 20%).

NMR (CDCl<sub>3</sub>) δ: 0.82 (t, 3H), 1.76 (q, 2H), 1.92 (m, 2H), 2.05 (m, 5H), 2.65 (t, 2H), 2.73 (t, 2H), 2.82 (d, 2H), 2.97 (s, 3H), 3.50 (d, 2H), 7.05 (m, 3H), 7.14-7.33 (m, 6H)

MS: m/z [MH<sup>+</sup>] 399.1; C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 399.2

20 Example 11

N-{3-[6-Ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-1-ethanesulfonamide acetate salt



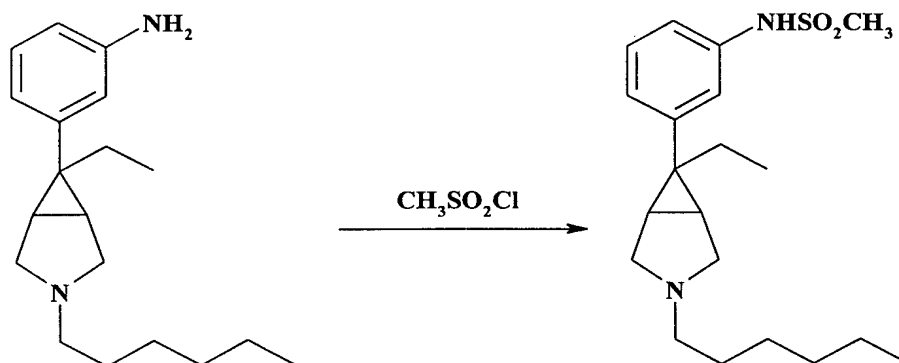
To a solution of 3-[6-ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 18, 500mg, 1.56mmol) in dichloromethane (20ml), at 0°C under nitrogen was added pyridine (0.20 ml, 2.6 mmol) then dropwise over 5 minutes ethanesulfonylchloride (0.20 ml, 0.27g, 2.1 mmol). The mixture was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (25 g) column chromatography eluting with 50:50:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil. This was further purified by preparative HPLC (condition 3). Combination and evaporation of pure fractions gave the title compound as a white solid (120mg, 17%).

NMR (CDCl<sub>3</sub>) δ: 0.80 (t, 3H), 1.32 (t, 3H), 1.74 (q, 2H), 1.89 (m, 2H), 1.99 (m, 5H), 2.62 (t, 2H), 2.72 (t, 2H), 2.81 (d, 2H), 3.08 (q, 2H), 3.43 (d, 2H), 6.97 (d, 1H), 7.07-7.37 (m, 8H)

MS: m/z [MH<sup>+</sup>] 413.1; C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 413.2

### Example 12

N-[3-(6-Ethyl-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



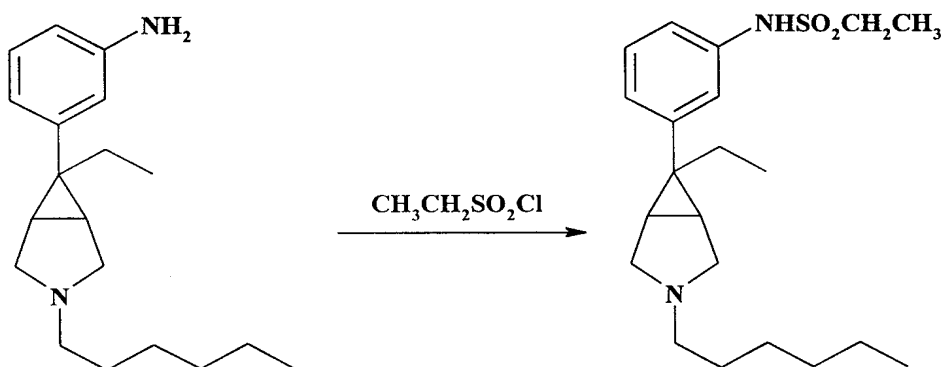
To a solution of 3-(6-ethyl-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 20, 500 mg, 1.56 mmol) in pyridine (5 ml) at 0°C under nitrogen was added dropwise over 5 minutes methanesulfonylchloride (0.20 ml, 0.30 g, 2.6 mmol). The mixture was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (25 g) column chromatography eluting with 50:50:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (180 mg, 33%).

NMR (CDCl<sub>3</sub>) δ: 0.85 (m, 6H), 1.27 (m, 6H), 1.44 (m, 2H), 1.77 (m, 2H), 1.94 (q, 2H), 2.43 (m, 2H), 2.81 (m, 2H), 2.98 (m, 2H), 2.99 (s, 3H), 7.00-7.13 (m, 3H), 7.24 (t, 1H).

MS (electrospray): m/z [MH<sup>+</sup>]; 365.1 C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 365.2

### 15 Example 13

N-[3-(6-Ethyl-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide



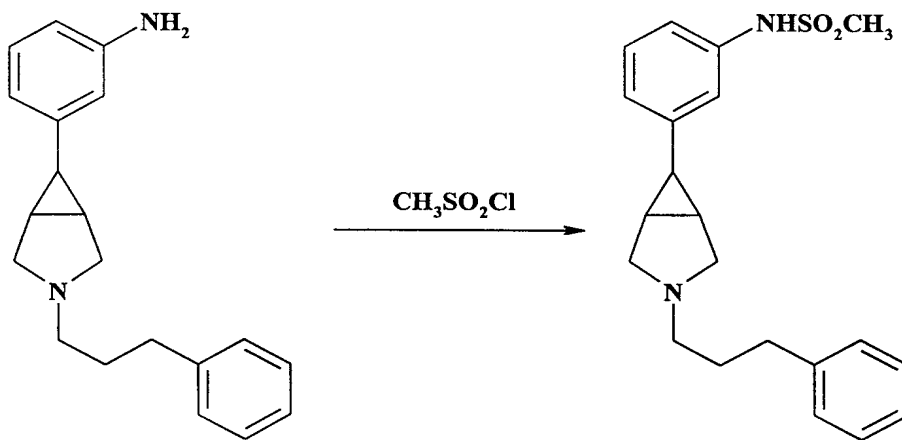
To a solution of 3-[6-ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 20, 500 mg, 1.56 mmol) in pyridine (5 ml), at 0°C under nitrogen was added dropwise over 5 minutes ethanesulfonylchloride (0.25 ml, 0.34 g, 2.6 mmol). The mixture was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (25 g) column chromatography eluting with 50:50:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (150 mg, 31%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.80 (t, 3H), 0.88 (t, 3H), 1.29 (m, 6H), 1.35 (t, 3H), 1.44 (m, 2H), 1.77 (m, 2H), 1.93 (q, 2H), 2.45 (t, 2H), 2.82 (m, 2H), 2.97 (d, 2H), 3.10 (q, 2H), 7.02-7.29 (m, 4H)

MS (electrospray):  $m/z$  [MH<sup>+</sup>] 379.1; C<sub>21</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 379.2

#### Example 14

#### 15 N-[3-(3-{3-Phenylpropyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



To a solution of 3-[3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 25, 34 mg, 0.11 mmol) in dichloromethane (2 ml) at 0°C under nitrogen was added pyridine (20  $\mu$ l, 0.24 mmol) then methanesulfonylchloride (13 mg, 10  $\mu$ l, 0.11 mmol). The mixture was allowed to warm to room temperature and was stirred for 1.5 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica (5 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution



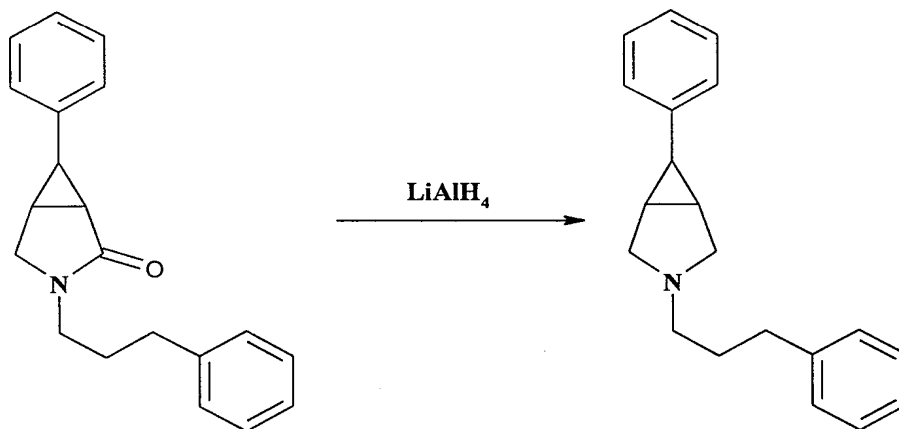
(0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (29 mg, 71%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.66 (s, 2H), 1.80 (m, 2H), 2.26 (s, 1H), 2.41 (d, 2H), 2.47 (t, 2H), 2.65 (t, 2H), 3.00 (s, 3H), 3.19 (d, 2H), 6.85 (d, 1H), 6.90 (s, 1H), 6.98 (d, 1H), 7.20 (m, 4H), 7.29 (m, 2H)

MS:  $m/z$  [MH<sup>+</sup>] 371.0; C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 371.2

### Example 15

#### 3-Hexyl-6-phenyl-3-azabicyclo[3.1.0]hexane



To a solution of 3-hexyl-6-phenyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 27, 40 mg, 0.15 mmol) in anhydrous tetrahydrofuran (2 ml) at room temperature under nitrogen, was added dropwise a solution of lithium aluminium hydride 1.0 M in tetrahydrofuran (0.3 ml, 0.3 mmol), then the mixture was heated to 60°C for 4 hours, cooled and stirred at room temperature for 64 hours. Water (30 ml) was carefully added, then the mixture was extracted with ethyl acetate (2 x 25 ml). The combined extracts were washed with water (30 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (1.5 g) column chromatography eluting with 80:20:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a pale yellow oil (14 mg, 38%).

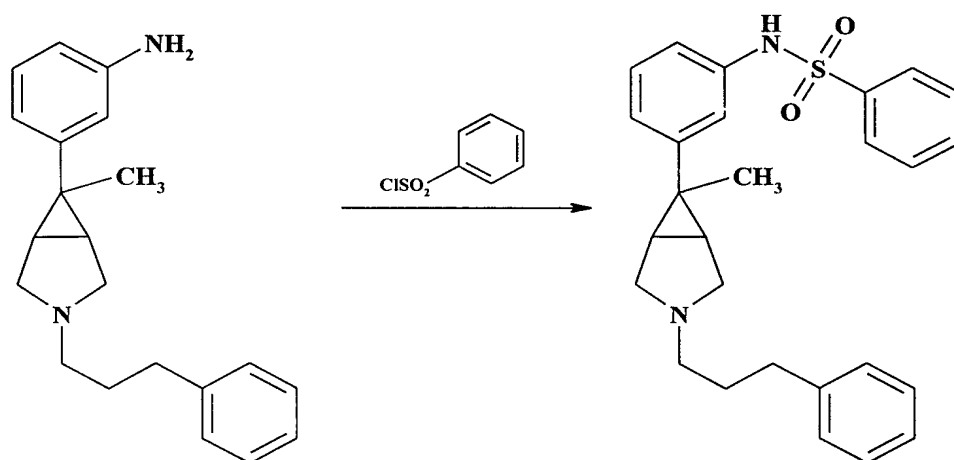
NMR (CDCl<sub>3</sub>)  $\delta$ : 0.90 (t, 3H), 1.30 (m, 6H), 1.44 (m, 2H), 1.65 (s, 2H), 2.16 (t, 1H), 2.42 (m, 4H), 3.19 (d, 2H), 7.04 (d, 2H), 7.12 (m, 1H), 7.24 (m, 2H)

MS (APCI):  $m/z$  [MH<sup>+</sup>] 244.4; C<sub>17</sub>H<sub>25</sub>N + H requires 244.2

Example 16

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-  
benzenesulfonamide acetate salt

5



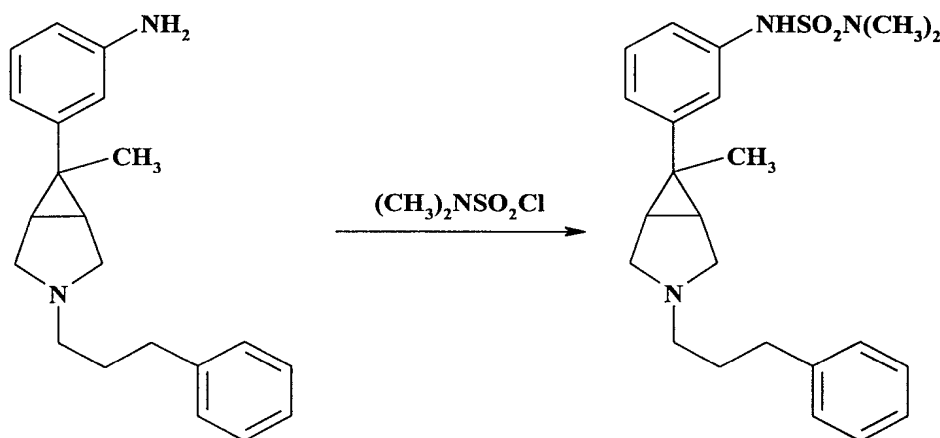
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added  
 10 benzenesulfonylchloride (172 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 hours. Water (5 ml) and dichloromethane (5 ml) were added, and the mixture was stirred for 30 minutes. The organic phase was washed further with water (5 ml) for 30 minutes, separated, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with 20:80:1 ethyl  
 15 acetate:hexane:ammonia solution (0.880), then 50:50:1 ethyl acetate:hexane:ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (5 mg, 2%).

20 NMR (CDCl<sub>3</sub>) δ: 1.39 (s, 3H), 1.84 (s, 2H), 1.89 (m, 2H), 2.06 (s, 3H), 2.65 (m, 4H), 2.90 (d, 2H), 3.23 (br.d, 2H), 6.89 (m, 2H), 6.97 (d, 1H), 7.07-7.35 (m, 6H), 7.43 (m, 2H), 7.52 (m, 1H), 7.73 (d, 2H)

MS (electrospray): m/z [MH<sup>+</sup>] 447.2; C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 447.2

Example 17

N,N-Dimethyl-N'-{3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}sulfamide acetate salt



5

To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added dimethylsulfamoyl chloride (140 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 hours. Water (5 ml) and dichloromethane (5 ml) were added, and the mixture was stirred for 30 minutes. The organic phase was washed further with water (5 ml) for 30 minutes, separated, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with ethyl acetate:hexane:ammonia solution (0.880) (20:80:1 then 50:50:1). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (7 mg, 3%).

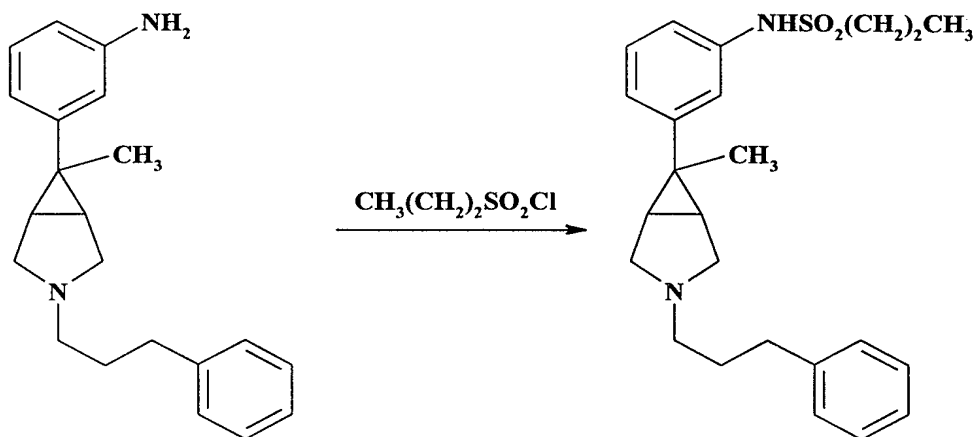
NMR (CDCl<sub>3</sub>) δ: 1.46 (s, 3H), 1.89 (m, 2H), 1.94 (s, 2H), 2.06 (s, 3H), 2.66 (m, 4H), 2.84 (s, 6H), 2.92 (m, 2H), 3.27 (br.d, 2H), 6.95-7.07 (m, 4H), 7.14-7.33 (m, 5H).

MS (electrospray): m/z [MH<sup>+</sup>] 414.3; C<sub>23</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 414.2.

Example 18

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}propanesulfonamide acetate salt

25



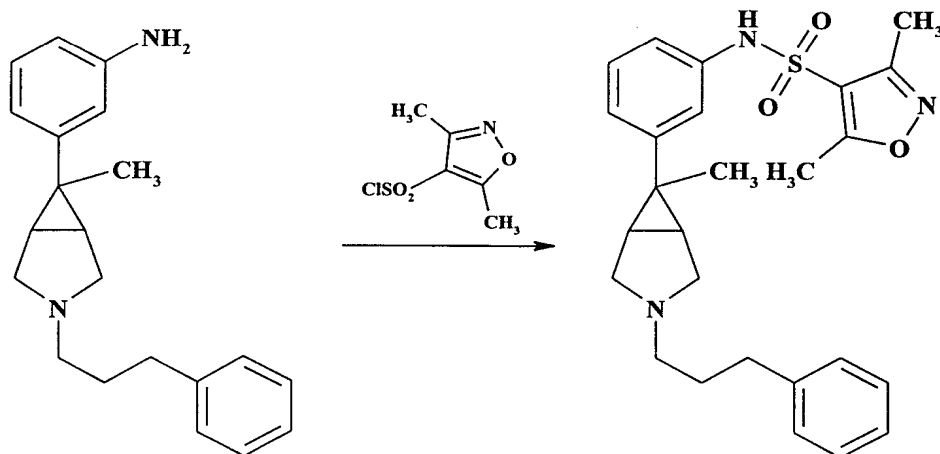
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added n-propanesulfonyl chloride (140 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 hours. Water (5 ml) and dichloromethane (5 ml) were added, and the mixture was stirred for 30 minutes. The organic phase was washed further with water (5 ml) for 30 minutes, separated, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with ethyl acetate:hexane:ammonia solution (0.880) (20:80:1 then 50:50:1). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (11 mg, 4%).

NMR (CDCl<sub>3</sub>) δ: 1.04 (t, 3H), 1.50 (s, 3H), 1.84 (m, 6H), 2.06 (s, 3H), 2.54-2.70 (m, 4H), 2.95 (d, 2H), 3.08 (m, 4H), 7.00-7.12 (m, 3H), 7.12-7.32 (m, 6H).

MS (electrospray): m/z [MH<sup>+</sup>] 413.3; C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 413.2.

#### Example 19

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide acetate salt



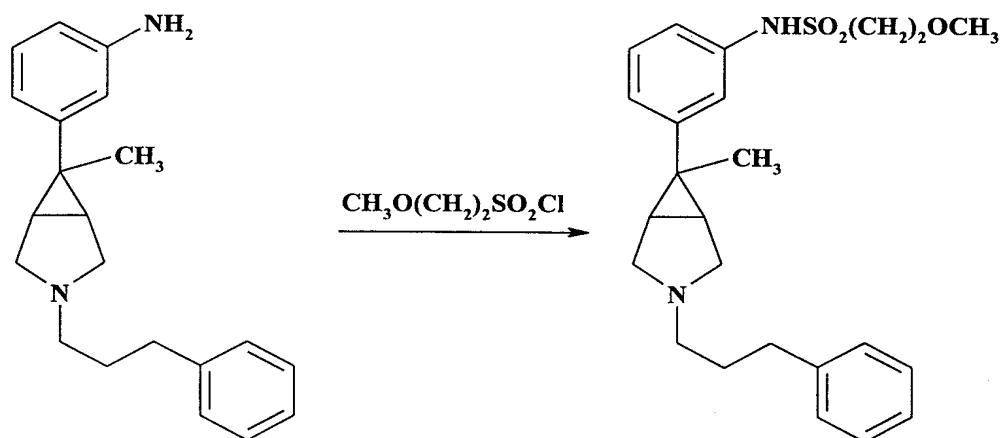
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added  
 5 3,5-dimethylisoxazolesulfonyl chloride (190 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 h. Water (5 ml) and dichloromethane (5 ml) were added, and the mixture stirred for 10 minutes. The organic phase was washed further with water (5 ml), separated, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with ethyl acetate:hexane:ammonia  
 10 solution (0.880) (20:80:1 then 60:40:1). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (18 mg, 6%).

NMR (CDCl<sub>3</sub>) δ: 1.42 (s, 3H), 1.87 (br.s, 2H), 1.95 (m, 2H), 2.09 (s, 3H), 2.25 (s, 3H),  
 15 2.43 (s, 3H), 2.55-2.76 (m, 6H), 2.95 (m, 2H), 6.91 (d, 1H), 7.00 (s, 1H), 7.05 (d, 1H), 7.13-7.34 (m, 6H)

MS (electrospray): m/z [MH<sup>+</sup>] 466.3; C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 466.2

#### Example 20

20 N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-2-methoxy-1-ethanesulfonamide



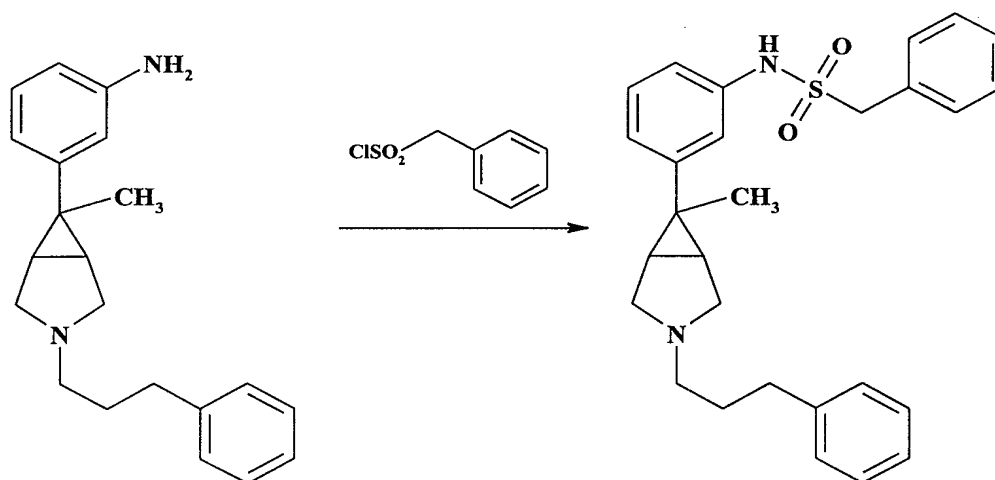
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added 2-methoxy-1-ethanesulfonyl chloride (J. Chem. Soc., 1968, 2895; 155 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 hours. Water (5 ml) and dichloromethane (5 ml) was added, and the mixture stirred for 10 minutes. The organic phase was washed further with water (5 ml), separated, dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with ethyl acetate:hexane:ammonia solution (0.880) (20:80:1 then 60:40:1). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (3 mg, 1%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.55 (s, 3H), 1.82 (m, 4H), 2.55 (m, 2H), 2.66 (t, 2H), 2.80-3.05 (br.m, 4H), 3.23 (t, 2H), 3.42 (s, 3H), 3.84 (t, 2H), 7.00-7.33 (m, 9H)

MS (electrospray):  $m/z$  [ $\text{MH}^+$ ] 429.3;  $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 429.2

### Example 21

N-{3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-(phenyl)methanesulfonamide acetate salt



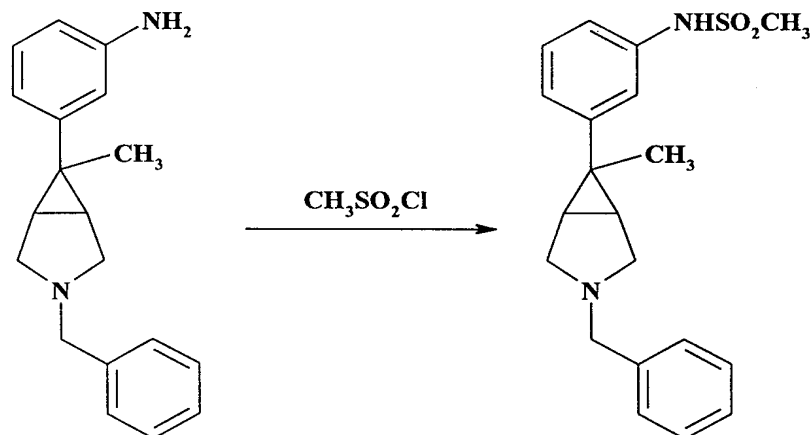
To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 200 mg, 0.65 mmol) in pyridine (2 ml) under nitrogen at 0°C was added  $\alpha$ -toluenesulfonyl chloride (186 mg, 0.98 mmol), then the mixture was stirred at room temperature for 16 hours. Water (5 ml) and dichloromethane (5 ml) were added and the mixture was stirred for 10 minutes. The organic phase was washed further with water (5 ml), separated, dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with ethyl acetate:hexane:ammonia solution (0.880) (20:80:1 then 60:40:1). Product-containing fractions were combined and concentrated *in vacuo*. The residue was further purified by preparative HPLC (condition 4). Combination and evaporation of appropriate fractions gave the title compound as a pale brown solid (3 mg, 1%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (s, 3H), 1.87 (m, 4H), 2.06 (s, 3H), 2.65 (m, 4H), 2.96 (d, 2H), 3.16 (br.d, 2H), 4.32 (s, 2H), 6.93-7.06 (m, 3H), 7.14-7.40 (m, 11H)

MS (electrospray):  $m/z$  [ $\text{MH}^+$ ] 461.3;  $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 461.2

#### Example 22

N-[3-(3-Benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



To a solution of 3-(3-benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 30, 1.58 g, 5.68 mmol) in pyridine (10ml ) under nitrogen at 0°C was added  
 5 methanesulphonyl chloride (0.66 ml, 8.52 mmol) dropwise to the solution, and the mixture was stirred for 14 hours at room temperature. The pyridine was evaporated *in vacuo* and the residue was partitioned between dichloromethane (50 ml) and dilute aqueous sodium hydrogen carbonate solution (1 M, 50 ml). The layers were separated and the organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified  
 10 by silica (60 g) column chromatography eluting with ethyl acetate:hexane (5:95) then ethyl acetate:hexane:triethylamine (5:95:0.1 increasing to 80:20:0.1). Appropriate fractions were combined and concentrated *in vacuo* to give the title compound as an off-white solid (1 g, 50%).

mp 117-118°C

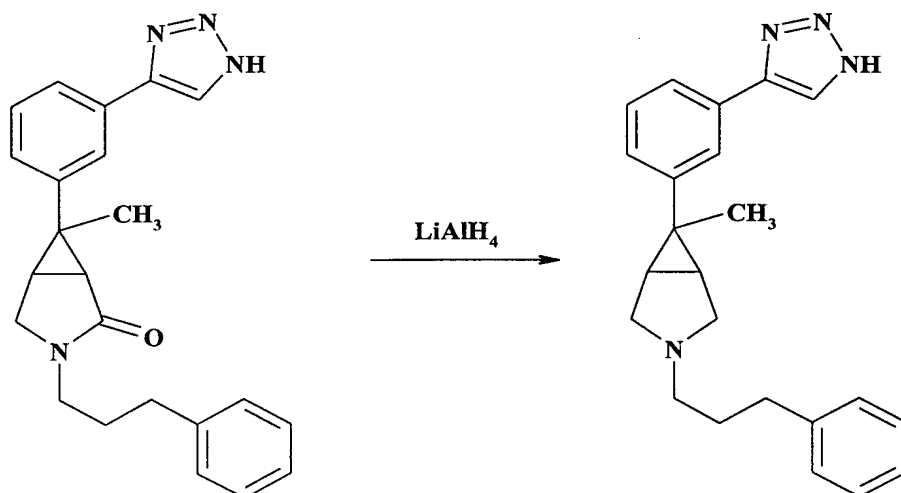
15 NMR (CDCl<sub>3</sub>) δ: 1.62 (s, 3H), 1.77 (s, 2H), 2.83 (d, 2H), 3.00 (s, 3H), 3.07 (d, 2H), 3.68 (s, 2H), 6.27 (br.s, 1H), 7.01 (d, 1H), 7.08 (m, 2H), 7.24-7.33 (m, 6H)

MS (thermospray): m/z [MH<sup>+</sup>] 356.9; C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 357.2

### Example 23

20 6-Methyl-3-(3-phenylpropyl)-6-[3-(1H-1,2,3-triazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexane





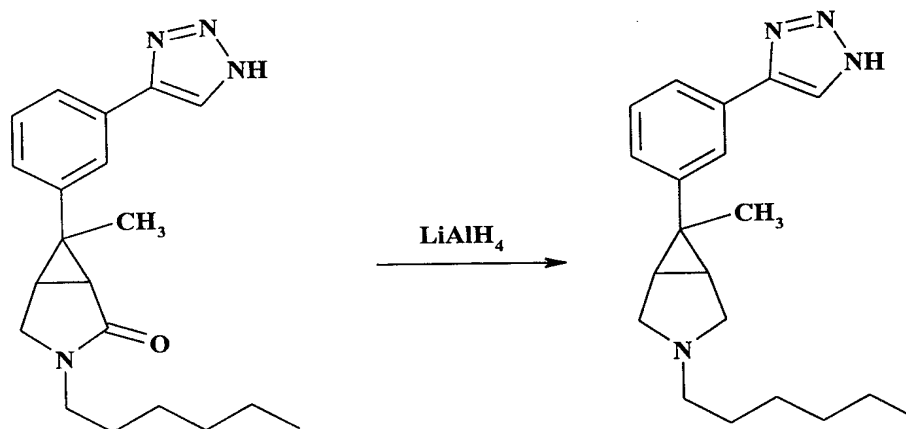
To a solution of 6-methyl-3-(3-phenylpropyl)-6-[3-(1H-1,2,3-triazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one (Preparation 41, 32 mg, 0.087 mmol) in tetrahydrofuran (2 ml) at room temperature was added lithium aluminium hydride (0.43 ml, 0.43 mmol, 1.0 M in THF) dropwise over a few minutes. The mixture was stirred at room temperature for 6 hours and then quenched by the cautious addition of 2N sodium hydroxide (0.5 ml) at 0°C. Excess solid sodium hydrogen carbonate and ethyl acetate (5 ml) were then added and the mixture was stirred rapidly for 30 minutes and then filtered through celite washing with ethyl acetate. The solvent was evaporated *in vacuo* and the crude residue was purified by silica column chromatography eluting first with hexane:ethyl acetate (1:1) and then hexane:ethyl acetate: ammonia solution (0.880) (10:90:1) to afford the title compound as a colourless oil (15.0 mg, 48%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.38 (s, 3H), 1.79-1.90 (m, 4H), 2.50 (t, 2H), 2.65 (t, 2H), 2.84 (m, 2H), 3.03 (m, 2H), 7.17-7.40 (m, 7H), 7.60 (d, 1H), 7.74 (br. s, 1H), 7.97 (s, 1H).

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 359.4; C<sub>23</sub>H<sub>26</sub>N<sub>4</sub> + H requires 359.2.

#### Example 24

3-Hexyl-6-methyl-6-[3-(1H-1,2,3-triazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexane



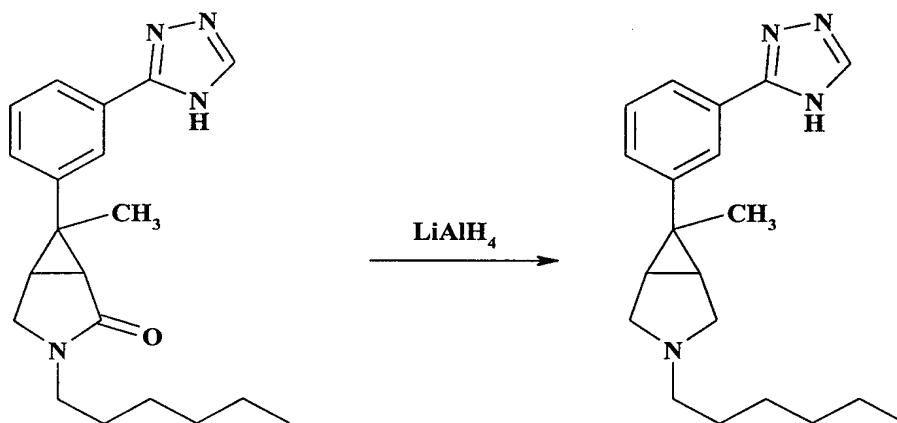
To a solution of 3-hexyl-6-methyl-6-[3-(1H-1,2,3-triazol-4-yl)phenyl]-3-azabicyclo[3.1.0]-  
 hexan-2-one (Preparation 40, 2.88 mmol) in tetrahydrofuran (25 ml) at 0°C was added  
 5 lithium aluminium hydride (5.8 ml, 5.76 mmol, 1.0M in THF) dropwise over a few  
 minutes. The mixture was stirred at room temperature for 2 hours and then quenched by the  
 cautious addition of 2N sodium hydroxide (3 ml) at 0°C. Ethyl acetate (15 ml) was then  
 added and the mixture was stirred rapidly for 30 minutes and then filtered through celite  
 washing with ethyl acetate. The solvent was evaporated *in vacuo* and the crude residue was  
 10 purified by silica column chromatography eluting with hexane:ethyl acetate (1:1) then  
 ethyl acetate:methanol:ammonia solution (0.880) (95:5:1) to afford the title compound  
 (301mg, 32% over 2 steps) as a colourless oil.

NMR (CDCl<sub>3</sub>) δ: 0.85-0.95 (m, 3H), 1.25-1.40 (m, 6H), 1.42-1.55 (m, 2H), 1.58 (s, 3H),  
 1.84 (m, 2H), 2.46 (m, 2H), 2.84-3.00 (4H, m), 7.23-7.40 (m, 2H), 7.58 (d, 1H), 7.76 (br. s,  
 15 1H), 7.98 (s, 1H).

MS (thermospray): m/z [MH<sup>+</sup>] 325.0; C<sub>20</sub>H<sub>28</sub>N<sub>4</sub> + H requires 325.2.

### Example 25

3-Hexyl-6-methyl-6-[3-(4H-1,2,4-triazol-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane



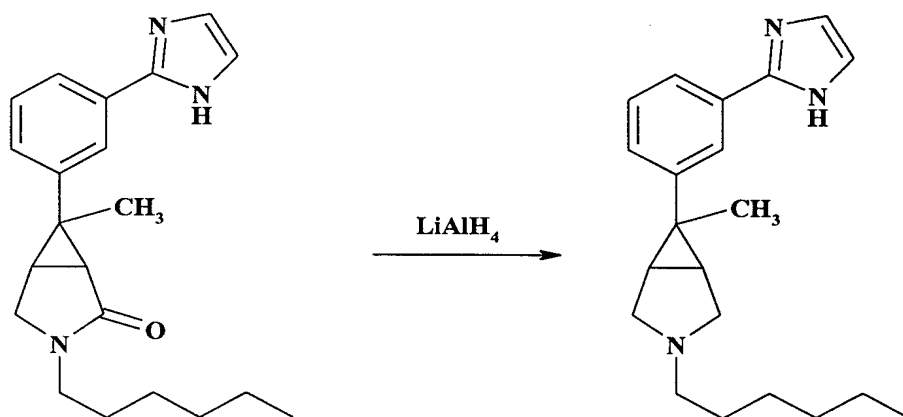
To a solution of 3-hexyl-6-methyl-6-[3-(4H-1,2,4-triazol-3-yl)phenyl]-3-azabicyclo[3.1.0]-  
 5 hexan-2-one (Preparation 43, 220 mg, 0.65 mmol) in tetrahydrofuran (5 ml) at room  
 temperature was added lithium aluminium hydride (1.3 ml, 1.30 mmol, 1.0M in THF)  
 dropwise over a few minutes. The mixture was then heated under reflux for 2 hours and  
 then cooled to 0°C. 2N sodium hydroxide (1.0 ml) was added cautiously followed by ethyl  
 acetate (10 ml) and the mixture was stirred rapidly for 30 minutes, then filtered through  
 celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica column  
 10 chromatography eluting with ethyl acetate:methanol:ammonia solution (0.880) (80:20:1) to  
 afford the title compound (190 mg, 90%) as a colourless oil.

NMR (CDCl<sub>3</sub>) δ: 0.82-0.92 (m, 3H), 1.25-1.38 (m, 6H), 1.40 (s, 3H), 1.50-1.65 (m, 2H),  
 1.99 (m, 2H), 2.70 (m, 2H), 2.85 (m, 2H), 3.46 (m, 2H), 7.18-7.38 (m, 2H), 7.89-7.92 (m,  
 2H), 8.18 (s, 1H).

15 MS (thermospray): *m/z* 325.1 [MH<sup>+</sup>]; C<sub>20</sub>H<sub>28</sub>N<sub>4</sub> + H requires 325.2

### Example 26

3-Hexyl-6-[3-(1H-imidazol-2-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]hexane



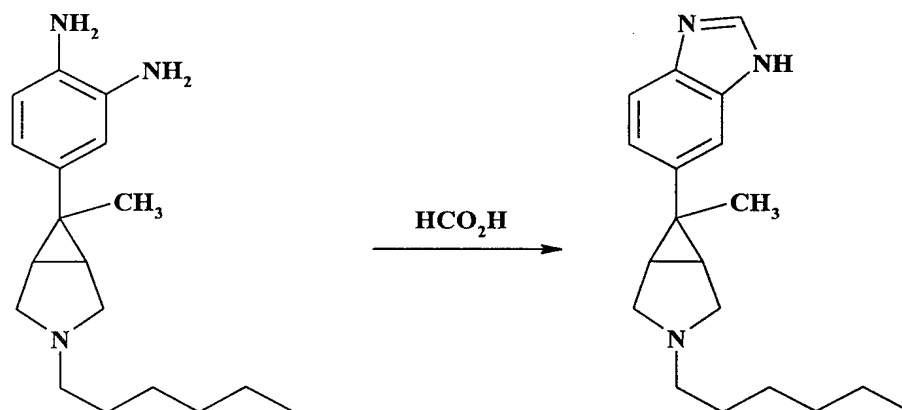
To a solution of 3-hexyl-6-[3-(1H-imidazol-2-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]-  
hexan-2-one (Preparation 44, 190 mg, 0.56 mmol) in tetrahydrofuran (5 ml) at room  
5 temperature was added lithium aluminium hydride (1.1 ml, 1.12 mmol, 1.0 M in THF)  
dropwise over a few minutes. The mixture was heated under reflux for 1 hour and then  
cooled to 0°C. 2N sodium hydroxide (1.0 ml) was added cautiously followed by ethyl  
acetate (10 ml) and the mixture was stirred rapidly for 30 minutes, then filtered through  
celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica column  
10 chromatography eluting with ethyl acetate:methanol: ammonia solution (0.880) (90:10:1)  
to afford the title compound (140 mg, 74%) as a white solid.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85-0.95 (m, 3H), 1.24-1.36 (m, 6H), 1.39-1.45 (m, 2H), 1.50 (s, 3H),  
1.78 (m, 2H), 2.42 (m, 2H), 2.80 (m, 2H), 2.95 (m, 2H), 7.10-7.35 (m, 4H), 7.58 (d, 1H),  
7.79 (s, 1H)

15 MS (thermospray):  $m/z$  324.1 [MH<sup>+</sup>]; C<sub>21</sub>H<sub>29</sub>N<sub>3</sub> + H requires 324.2

### Example 27

5-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-1H-benzimidazole



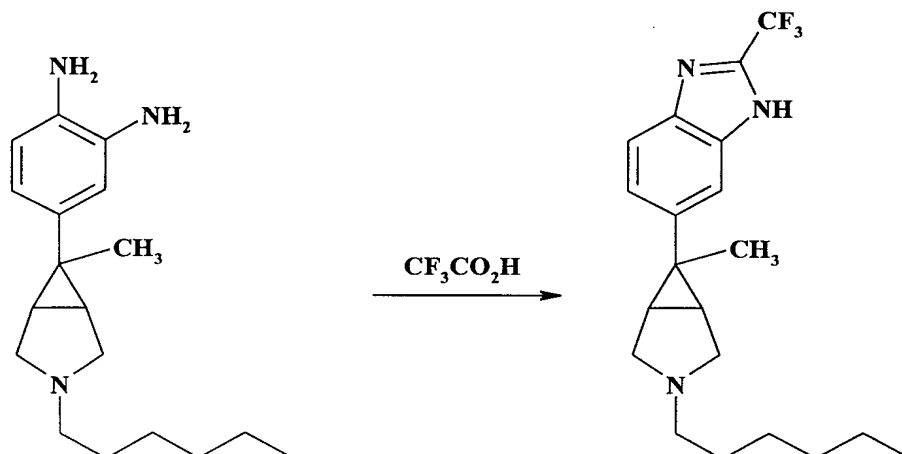
A solution of 2-amino-4-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 48, 112 mg, 0.39 mmol) in formic acid (2.0 ml) was heated under reflux for 1  
 5 h. The mixture was cooled, diluted with water (3 ml) and the pH adjusted to 10 with 5N sodium hydroxide. The aqueous layer was extracted with diethyl ether (3 x 5 ml) and ethyl acetate (2 x 5ml). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and the solvent removed *in vacuo*. The crude residue was purified by silica column chromatography eluting with ethyl acetate then ethyl acetate:methanol:ammonia solution  
 10 (0.880) (80:20:1) to afford the title compound (46 mg, 40%) as a colourless oil.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85-0.95 (m, 3H), 1.22-1.56 (m, 11H), 1.83 (m, 2H), 2.50 (t, 2H), 2.92-3.00 (m, 4H), 7.20 (d, 1H), 7.50 (s, 1H), 7.56 (d, 1H), 8.00 (s, 1H)

MS (thermospray):  $m/z$  298.2 [MH<sup>+</sup>]; C<sub>19</sub>H<sub>27</sub>N<sub>3</sub> + H requires 298.2.

#### 15 Example 28

5-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-2-(trifluoromethyl)-1H-benzimidazole



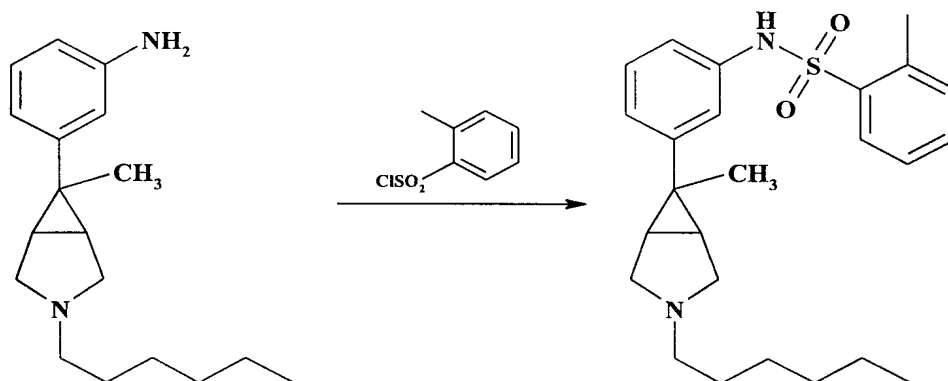
A solution of 2-amino-4-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 48, 99.0 mg, 0.345 mmol) in trifluoroacetic acid (2.0 ml) was heated under reflux for 1 hour. The mixture was cooled and the solvent was removed *in vacuo*. The residue was suspended in 2N sodium hydroxide (5 ml) and the aqueous layer was extracted with diethyl ether (3 x 5 ml). The combined extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography eluting with ethyl acetate to afford the title compound (67 mg, 54%) as a colourless oil.

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.85-0.95 (m, 3H), 1.25-1.52 (m, 8H), 1.56 (s, 3H), 1.83 (m, 2H), 2.50 (t, 2H), 2.92-3.00 (m, 4H), 7.30 (d, 1H), 7.56 (s, 1H), 7.62 (d, 1H)

MS (thermospray) :  $\text{M/Z} [\text{MH}^+]$  366.4;  $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_3 + \text{H}$  requires 366.2

### Example 29

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-2-methylbenzenesulfonamide



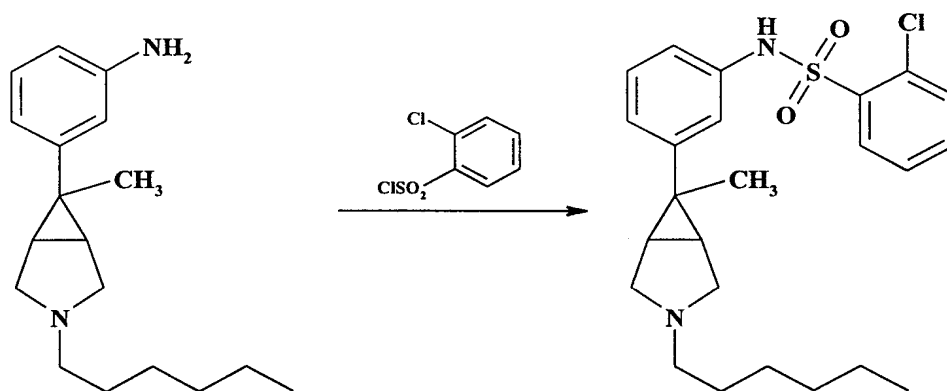
A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (5 ml) cooled at 0°C was treated with 2-methylbenzenesulfonyl chloride (0.08 g, 0.44 mmol). The reaction mixture was stirred at room temperature for 3 h, water (30 ml) was added and the product was extracted with diethyl ether (30 ml x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and then concentrated *in vacuo*. The crude products were purified by preparative HPLC (condition 5) to give the acetate salt as a brown gum, (30 mg, 20%).

NMR (CDCl<sub>3</sub>, selected data for the acetate salt): 0.9 (m, 3H), 1.1 - 1.2 (m, 9H), 1.6 (m, 2H), 2.0 (m, 2H), 2.6 (s, 3H), 2.9 (m, 2H), 3.0 (m, 2H), 3.55 (m, 2H), 6.8 - 7.9 (m, 8H).

MS (ES) : M/Z (MH<sup>+</sup>) 427.3; C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 427.2.

#### Example 30

##### 2-Chloro-N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]benzenesulfonamide

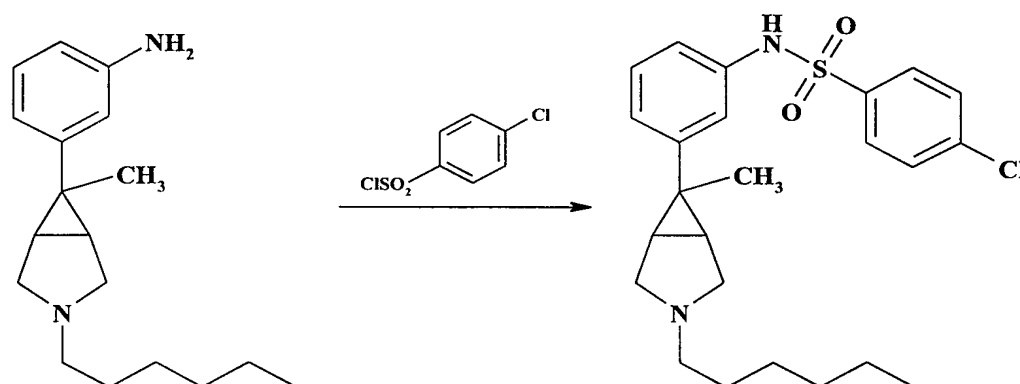


The title compound was prepared by the method of Example 29 substituting 2-methylbenzenesulfonyl chloride with 2-chlorobenzenesulfonyl chloride (90 mg, 0.44 mmol) to give a light brown gum (30 mg, 18%).

NMR (CDCl<sub>3</sub>, selected data for the acetate salt): 0.9 (m, 3H), 1.1 - 1.2 (m, 9H), 1.6 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.4 (m, 2H), 6.85-6.95 (m, 2H), 7.05 (s, 1H), 7.1 (t, 1H), 7.4 (m, 1H), 7.5 - 7.6 (m, 2H), 8.0 (d, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 447.3; C<sub>24</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>S + H requires 447.2.

#### Example 31

4-Chloro-N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]benzenesulfonamide

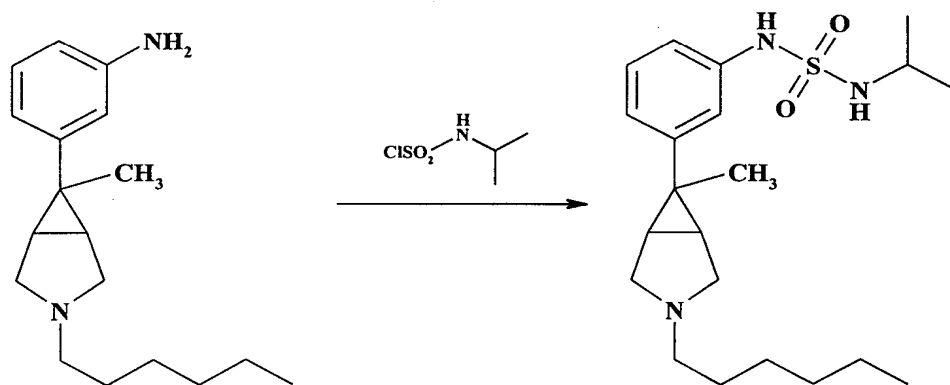
- 5 A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (5 ml) cooled at 0°C was treated with 4-chlorobenzenesulfonyl chloride (90 mg, 0.44 mmol). The reaction mixture was stirred at room temperature for 3 h, water (30 ml) was added and the product was extracted with diethyl ether (30 ml x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and then
- 10 concentrated *in vacuo*. The crude products were purified by preparative HPLC (condition 5). The acetate salt obtained was basified with saturated aqueous sodium hydrogen carbonate solution (20 ml) and extracted with dichloromethane (2 x 20 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a colourless oil, (20 mg, 13%).
- 15 NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.35 (m, 6H), 1.4 (s, 3H), 1.7 (m, 2H), 2.5 (m, 2H), 2.9 (m, 2H), 6.8 (d, 1H), 6.9 (s, 1H), 7.0 (d, 1H), 7.1 (t, 1H), 7.4 (d, 2H), 7.65 (d, 2H).

MS (ES) : M/Z (MH<sup>+</sup>) 447.3; C<sub>24</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>S + H requires 447.2.

20 Example 32

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-N'-isopropylsulfamide





The title compound was prepared by the method of Example 31 substituting 4-chlorobenzenesulfonyl chloride with 2-[(chlorosulfonyl)amino]propane (Preparation 49, 70 mg, 0.44 mmol) to give a colourless oil (20 mg, 14 %).

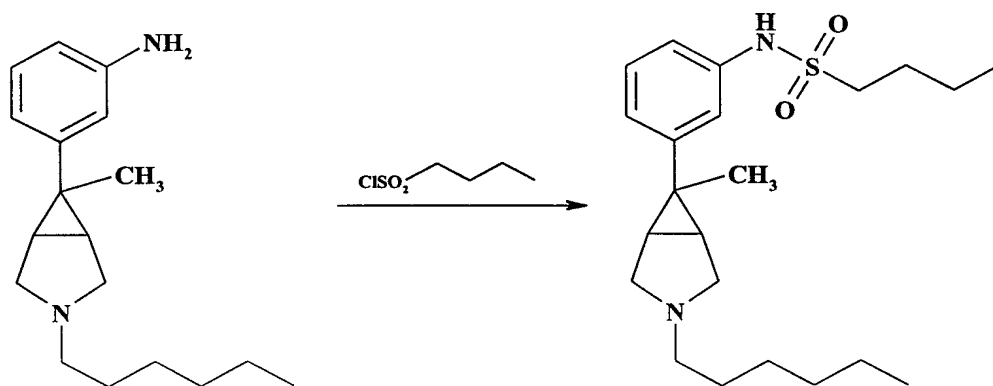
NMR (CDCl<sub>3</sub>, selected data for the acetate salt): 0.85 (m, 3H), 1.15 (d, 6H), 1.2-1.4 (m, 9H), 1.4 (m, 2H), 1.8 (m, 2H), 2.4 (m, 2H), 2.8 (m, 2H), 2.95 (m, 2H), 3.55 (m, 1H), 4.25 (br, 1H), 6.9-7.05 (m, 3H), 7.2, t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 394.3; C<sub>21</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 394.3.

10

### Example 33

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-butananesulfonamide



15

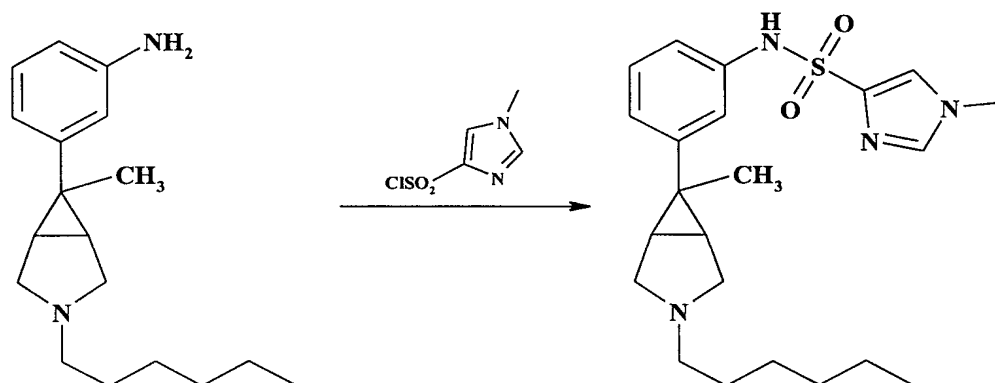
The title compound was prepared by the method of Example 31 substituting 4-chlorobenzenesulfonyl chloride with 1-butananesulfonyl chloride (69 mg, 0.44 mmol) to give a colourless oil (20 mg, 14 %).

MS (ES): M/Z (MH<sup>+</sup>) 393.3; C<sub>22</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 393.3.

Analytical HPLC purity: 95%, retention time 17.6 min (condition 6).

### Example 34

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide



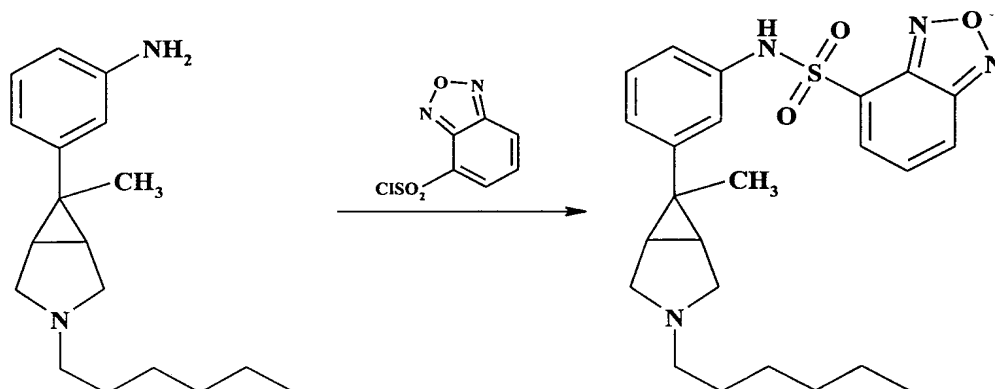
A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation  
 10 12, 0.10 g, 0.37 mmol) in pyridine (5 ml) cooled at 0°C was treated with 1-methyl-1H-  
 imidazole-4-sulfonyl chloride (0.08 g, 0.44 mmol). The reaction mixture was stirred at  
 room temperature for 3 h, water (30 ml) was added and the product was extracted with  
 dichloromethane (30 ml x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and then  
 concentrated *in vacuo*. The crude products were purified by preparative HPLC (condition  
 15 5). The acetate salt obtained was basified with saturated aqueous sodium hydrogen  
 carbonate solution (20 ml) and extracted with dichloromethane (2 x 20 ml). The combined  
 organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an off-white solid,  
 (30 mg, 20%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.9 (t, 3H), 1.2-1.35 (m, 6H), 1.4 (s, 3H),  
 20 1.65 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 2.95 (d, 2H), 3.65 (s, 3H), 6.9-7.2 (m, 4H), 7.3, (s,  
 1H), 7.45 (s, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 417.0; C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>S + H requires 417.2.

### Example 35

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-2,1,3-benzoxadiazole-4-sulphonamide



A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation  
 5 12, 0.10 g, 0.37 mmol) in pyridine (5 ml) cooled at 0°C was treated with 2,1,3-  
 benzoxadiazole-4-sulfonyl chloride (0.1 g, 0.44 mmol). The reaction mixture was stirred at  
 room temperature for 3 h, water (30 ml) was added and the product was extracted with  
 diethyl ether (30 ml x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and then  
 concentrated *in vacuo*. The crude products were purified by preparative HPLC (condition  
 10 1), to give the acetate salt as an off-white gum (14 mg, 8%).

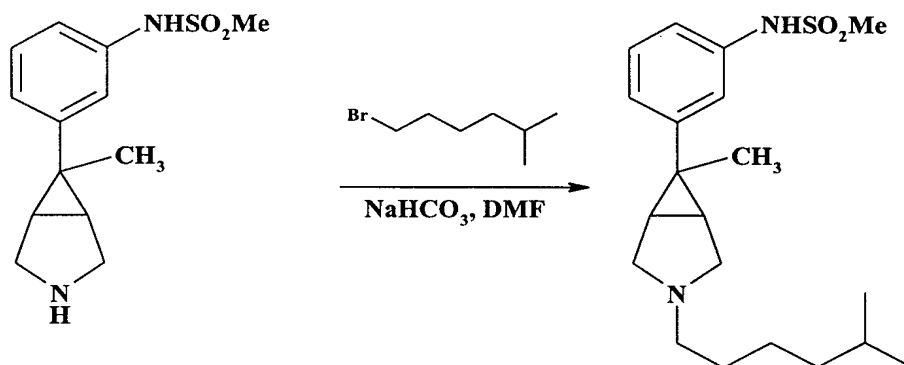
NMR (CDCl<sub>3</sub>, selected data for the acetate salt): 0.85 (t, 3H), 1.2-1.30 (m, 6H), 1.35 (s,  
 3H), 1.5 (m, 2H), 1.6 (m, 2H), 2.45 (m, 2H), 2.8- 2.95 (m, 4H), 3.65 (s, 3H), 3.7 (br, 1H),  
 6.8 (d, 1H), 6.85-6.95 (m, 2H), 7.0 (t, 1H), 7.45 (m, 1H), 7.9-8.1 (m, 2H).

MS (ES): M/Z (MH<sup>+</sup>) 455.3; C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>S + H requires 455.2.

15

### Example 36

N-{3-[6-Methyl-3-(5-methylhexyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide

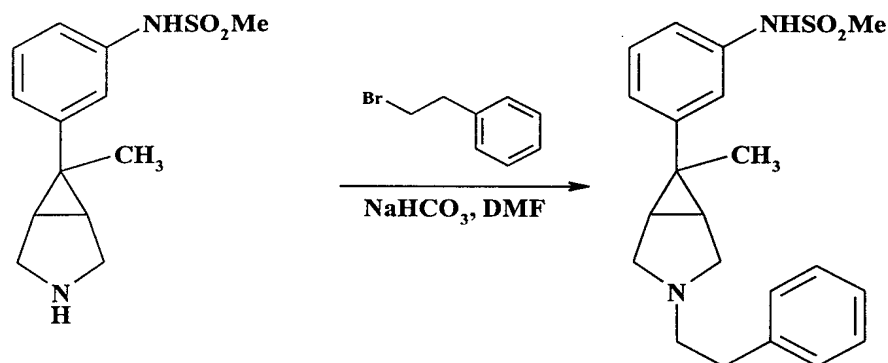


To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (63 mg, 0.75 mmol) and 1-bromo-5-methyl hexane (37 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (32 mg, 49%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (d, 6H), 1.15 - 1.6 (m, 8H), 1.5 (s, 3H), 1.75 (m, 2H), 2.5 (m, 2H), 2.8 - 3.0 (m, 4H), 3.0 (s, 3H), 7.0 - 7.1 (m, 3H), 7.2 (t, 1H).  
MS (ES): M/Z (MH<sup>+</sup>) 365.2; C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 365.2.

### Example 37

*N*-[3-(6-Methyl-3-phenethyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



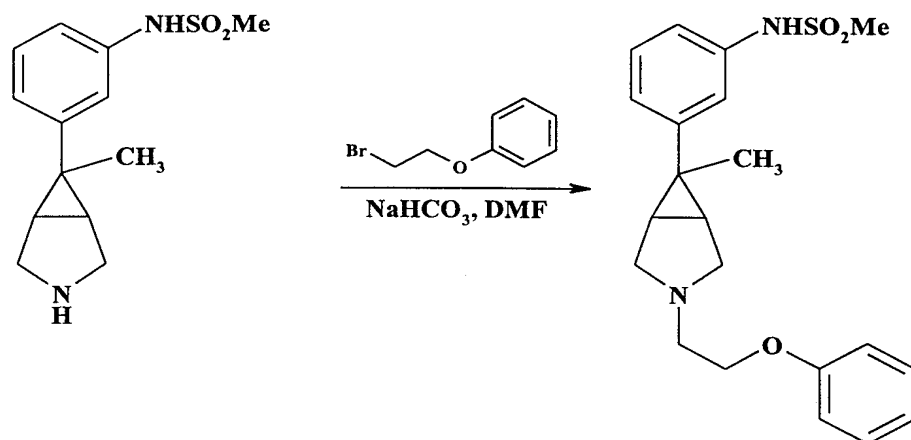
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 68 mg, 0.23 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (76 mg, 0.90 mmol) and (2-bromoethyl)benzene (46 mg, 0.25 mmol). The reaction mixture was heated for 17 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (3 x 6 ml). The combined organic extracts were dried over (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as a pale yellow oil (35 mg, 41%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.6 (s, 3H), 1.8 (m, 2H), 2.75 - 2.85 (m, 4H), 2.9 - 3.1 (m, 7H), 6.9 - 7.1 (m, 3H), 7.15 - 7.3 (m, 6H).

MS (ES) : M/Z (MH<sup>+</sup>): 371.0, C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 371.2.

### Example 38

*N*-{3-[6-Methyl-3-(2-phenoxyethyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



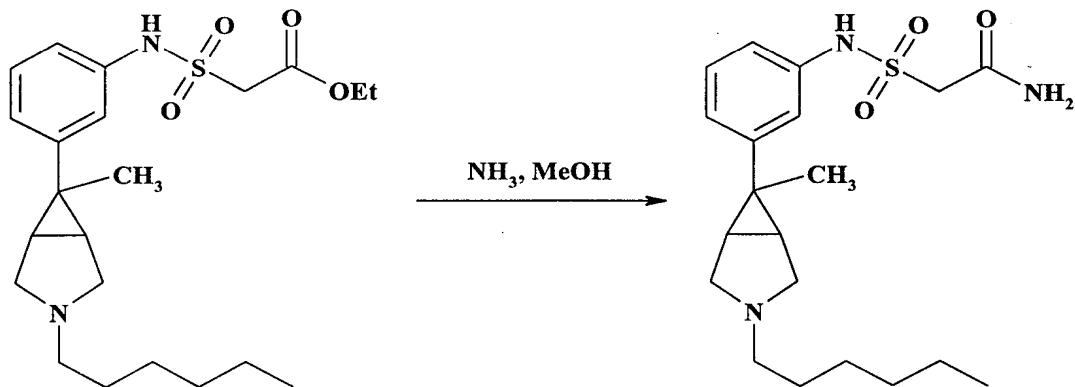
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (63 mg, 0.75 mmol) and 2-(bromoethoxy)benzene (42 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried over (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (41 mg, 59%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.8 (m, 2H), 2.9 - 3.1 (m, 9H), 4.05 (m, 2H), 6.85 - 6.95 (m, 3H), 7.0 - 7.1 (m, 3H), 7.2 - 7.35 (m, 3H).

MS (ES) : M/Z (MH<sup>+</sup>)387.3; C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 387.2.

### Example 39

2-[[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)anilino]sulfonyl]acetamide



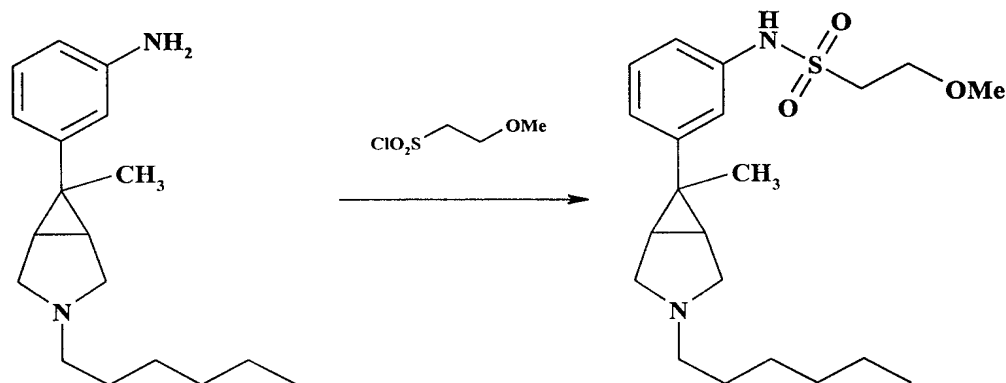
A solution of ethyl 2-([3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)anilino]sulfonyl}acetate (Example 41, 0.13 g, 0.38 mmol) in ammonia (2M in methanol,  
 5 3.0 ml, 1.5 mmol) was heated to 60°C for 12 h in a sealed tube. The mixture was cooled, concentrated *in vacuo* and then purified by chromatography on silica gel eluting with methanol : ethyl acetate (2 : 98) to give the product as a pale yellow foam (80 mg, 53%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.9 (m, 3H), 1.25 - 1.4 (m, 6H), 1.4 - 1.5 (m, 5H), 1.8 (m, 2H), 2.5 (m, 2H), 2.85 - 3.0 (m, 4H), 3.85 (s, 2H), 5.8 (br, 1H), 6.3 (br, 1H),  
 10 7.1 - 7.25 (m, 4H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 394.4;  $\text{C}_{20}\text{H}_{31}\text{N}_3\text{O}_3\text{S} + \text{H}$  requires 394.2.

#### Example 40

N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-2-methoxy-1-  
 15 ethanesulfonamide



To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.11 g, 0.40 mmol) in dichloromethane (1.5 ml) was added pyridine (64 mg) in dichloromethane (0.75 ml) and 2-methoxy-1-ethanesulfonyl chloride (J. F. King, J. Y. L. Lam, S. Kronieczny, J. Am. Chem. Soc., 1992, 114 (5), 1743; 0.96 g, 0.60 mmol).

5 The reaction mixture was stirred at room temperature for 16 h and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with ethyl acetate : 2M ammonia in methanol (99 : 1).

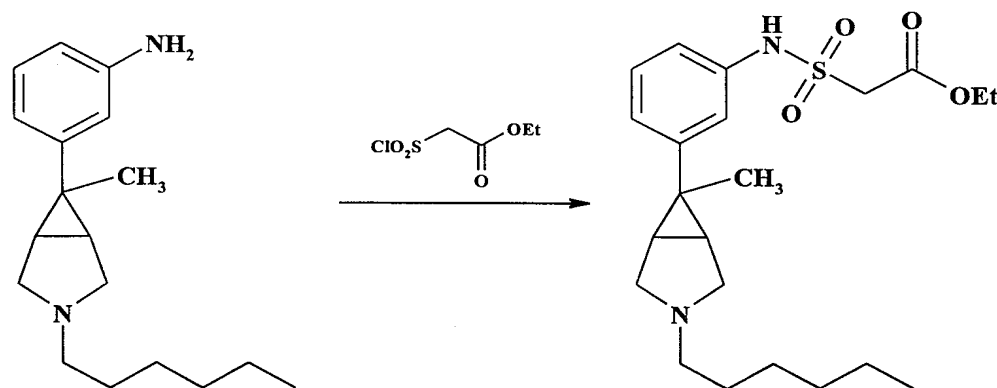
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.45 (m, 2H), 1.5 (s, 3H), 1.8 (m, 2H), 2.4 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.2 (m, 2H), 3.4 (s, 3H), 3.8  
10 (m, 2H), 6.95 - 7.15 (m, 3H), 7.25 (m, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 395.2; C<sub>21</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 395.2

#### Example 41

#### Ethyl 2-{[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)anilino]sulfonyl}acetate

15



To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.50 g, 1.84 mmol) in dichloromethane (5.0 ml) was added pyridine (0.27  
20 ml) in dichloromethane (2.5 ml) and ethyl (2-chlorosulfonyl)acetate (J. E. Oliver, A. B. DeMilo, Synthesis, 1975, 321, 0.48 g, 2.5 mmol). The reaction mixture was stirred at room temperature for 8 h, saturated aqueous sodium hydrogen carbonate solution (10 ml) was added, the organic extracts were separated and the aqueous layer was further extracted with dichloromethane (2 x 10 ml). The combined organic layers were dried (MgSO<sub>4</sub>) and  
25 concentrated *in vacuo*. The crude extracts were purified by chromatography on silica gel



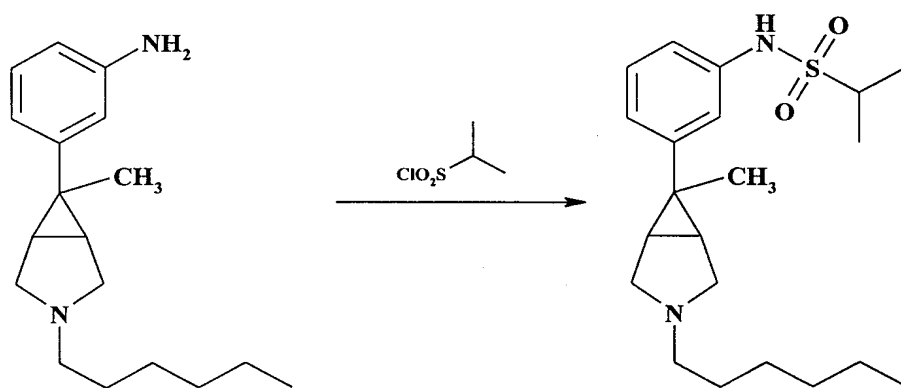
eluting with ethyl acetate : hexane (10 : 1) to give a colourless oil which solidified upon cooling (0.70 g, 91%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 9H), 1.4 (m, 2H), 1.5 (s, 3H), 1.7 (m, 2H), 2.4 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.85 (s, 2H), 4.25 (q, 2H), 7.05 - 7.2 (m, 4H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 423.2;  $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_4\text{S} + \text{H}$  requires 423.2

#### Example 42

##### N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-2-propanesulfonamide



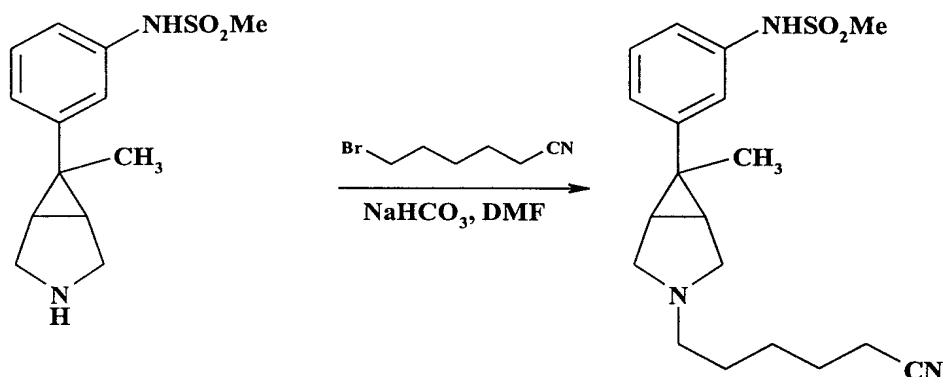
A solution of 3-(3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl)aniline (Preparation 12, 0.75 g, 0.28 mmol) in pyridine (1.5 ml) cooled at  $0^\circ\text{C}$  was treated with 2-propanesulfonyl chloride (0.05 g, 0.33 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the crude red residue was purified by chromatography on silica gel (5 g) eluting with hexane : ethyl acetate : 0.880 ammonia (50 : 50 : 0.5) to give the product as a light green gum (15 mg, 14%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.9 (t, 3H), 1.05 - 1.15 (m, 12H), 1.2 - 1.35 (m, 5H), 1.8 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.2 (m, 1H), 6.95 - 7.1 (m, 2H), 7.15 - 7.25 (m, 2H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 379.4;  $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 379.2.

#### Example 43

*N*-{3-[3-(5-Cyanopentyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



5

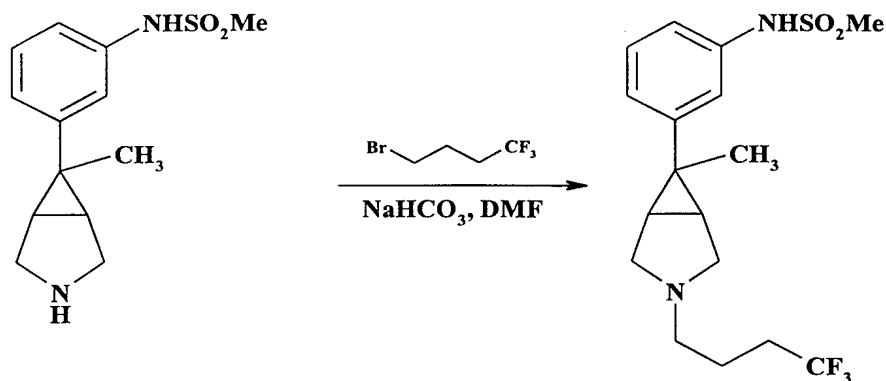
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (63 mg, 0.75 mmol) and 6-bromohexanenitrile (36 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (32 mg, 49%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.4 - 1.6 (m, 7H), 1.7 (m, 2H), 1.8 (m, 2H), 2.3 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 2.9 - 3.0 (m, 5H), 6.95 - 7.1 (m, 3H), 7.25 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 362.2; C<sub>19</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 362.2.

20 Example 44

*N*-{3-[6-Methyl-3-(4,4,4-trifluorobutyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



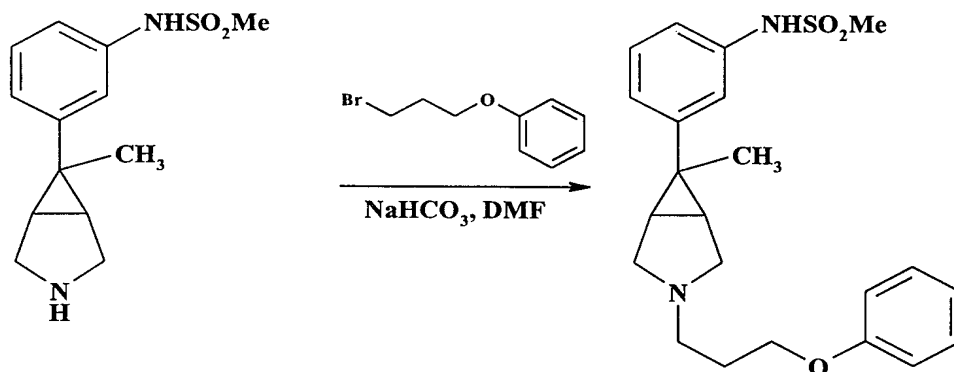
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (63 mg, 0.75 mmol) and 4-bromo-1,1,1-trifluorobutane (40 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, before addition of further 4-bromo-1,1,1-trifluorobutane (20 mg, 0.10 mmol). The reaction mixture was cooled to room temperature, diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (29 mg, 43%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.5 (s, 3H), 1.65 - 2.85 (m, 4H), 2.15 (m, 2H), 2.6 (m, 2H), 2.8 - 3.1 (m, 4H), 3.0 (s, 3H), 7.0 - 7.15 (m, 3H), 7.2 (m, 1H).

MS (ES) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 377.3;  $\text{C}_{17}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 377.2.

#### Example 45

*N*-{3-[6-Methyl-3-(3-phenoxypropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



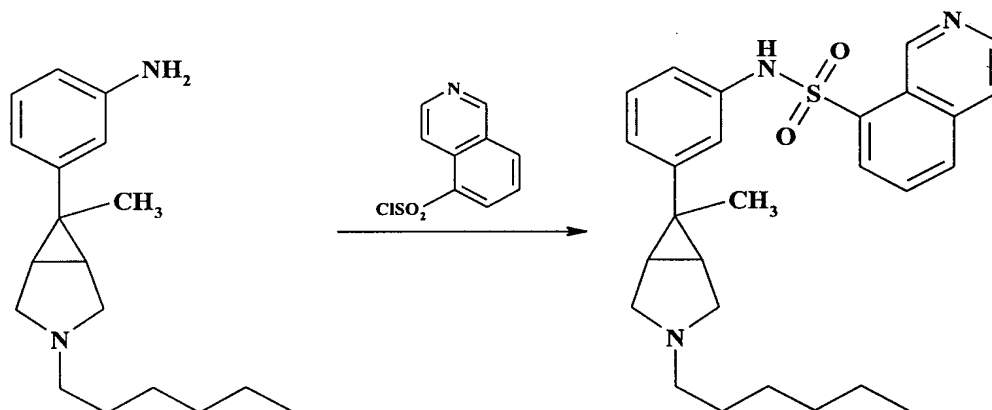
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate solution (63 mg, 0.75 mmol) and 3-phenoxypropyl bromide (45 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (10 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried over (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (40 mg, 55%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.55 (s, 3H), 1.8 (m, 2H), 1.95 (m, 2H), 2.65 (m, 2H), 2.9 (m, 2H), 3.0 (s, 3H), 3.05 (m, 2H), 4.0 (t, 2H), 6.85 - 6.95 (m, 3H), 7.0 - 7.1 (m, 3H), 7.2 - 7.35 (m, 3H).

MS (ES) : M/Z (MH<sup>+</sup>) 401.3; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 401.2.

#### Example 46

*N*-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-5-isoquinolinesulfonamide



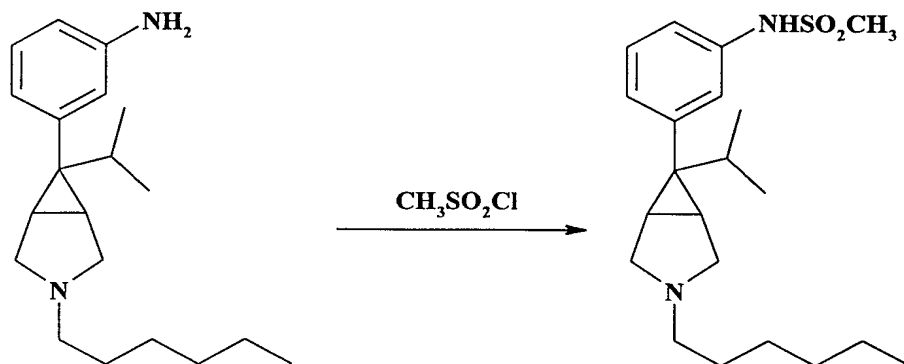
A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (10 ml) cooled at 0°C was treated with 5-isoquinolinesulfonyl chloride (0.10 g, 0.44 mmol). The reaction mixture was stirred at room temperature for 16 h before addition of more 5-isoquinolinesulfonyl chloride (0.05 g, 0.22 mmol). The reaction mixture was concentrated *in vacuo* and the crude red residue was dissolved in dichloromethane (20 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (20 ml), the aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (5 g) eluting with hexane : ethyl acetate : 0.88 ammonia (30 : 70 : 0.5 and then 0 : 100 : 0.5) to give the product as a yellow gum (90 mg, 52%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.35 (m, 9H), 1.3 - 1.6 (m, 4H), 2.45 (m, 2H), 2.8 - 3.0 (br, 3H), 6.75 (d, 1H), 6.8 (s, 1H), 6.9 (d, 1H), 7.0 (t, 1H), 7.6 (t, 1H), 8.15 (d, 1H), 8.3 - 8.4 (m, 2H), 8.6 (m, 1H), 9.3 (m, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 464.2; C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 464.2.

#### Example 47

20 N-[3-(3-Hexyl-6-isopropyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulphonamide



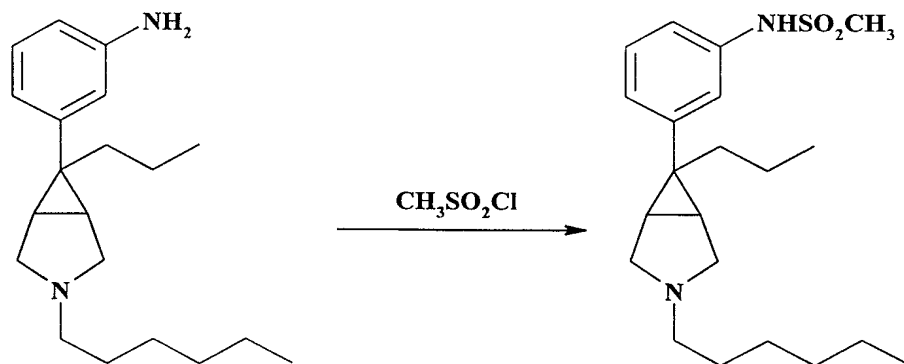
To a stirred solution of 3-(3-hexyl-6-isopropyl-3-azabicyclo[3.1.0]hex-6-yl)aniline (Preparation 61, 0.17 g, 0.57 mmol) in dichloromethane (5 ml) under nitrogen was added  
 5 pyridine (0.07 ml, 0.91 mmol) and the reaction mixture was cooled to  $-5^{\circ}\text{C}$ . Methanesulfonyl chloride (0.05 ml, 0.68 mmol) was added dropwise so that the internal temperature was maintained below  $-2^{\circ}\text{C}$ . The reaction mixture was stirred for 3 h and then treated with water (40 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*  
 10 to give an amber oil. The crude product was purified by chromatography on a Biotage Flash12M<sup>TM</sup> cartridge packed with silica gel (8 g), the product was eluted with ethyl acetate : 0.880 ammonia (99 : 1) to give the purified product (0.12 g, 56%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.8 (d, 6H), 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 2.4 (m, 2H), 2.8 (m, 2H), 2.9 (m, 2H), 3.0 (s, 3H), 7.0- 7.25 (m, 4H),

15 MS (ES) :  $\text{M/Z (MH}^+)$  379.0;  $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 379.2.

#### Example 48

N-[3-(3-Hexyl-6-propyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulphonamide



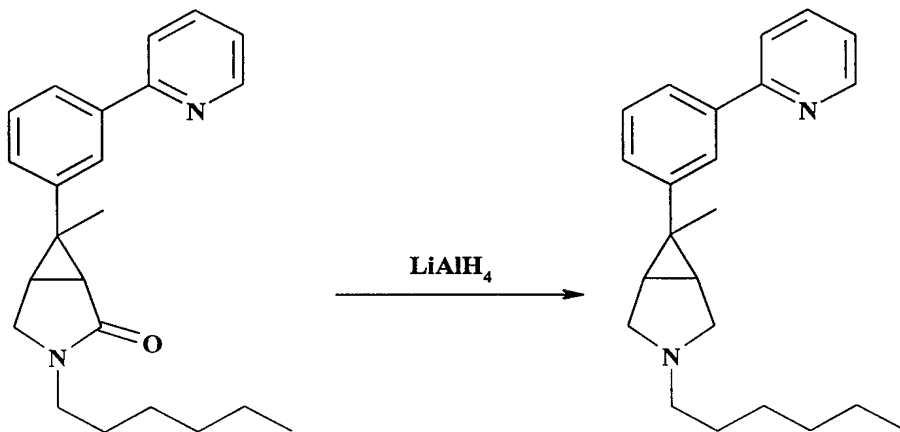
To a stirred solution of 3-(3-hexyl-6-propyl-3-azabicyclo[3.1.0]hex-6-yl)aniline (Preparation 66, 1.0 g, 3.32 mmol) in dichloromethane (52 ml) under nitrogen was added pyridine (53  $\mu$ l, 6.56 mmol) and the reaction mixture was cooled to 0°C. Methanesulfonyl chloride (280  $\mu$ l, 3.61 mmol) was added dropwise and then the reaction mixture was stirred at room temperature for 16 h. The crude residue was dissolved in dichloromethane : 2M ammonia solution in methanol (80:20), filtered through a pad of silica gel and then through a syringe filter and concentrated *in vacuo* to give the hydrochloride salt which was then treated with 0.880 ammonia : water (1 : 3) and extracted with diethyl ether. The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give an orange oil (1.18 g, 94%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.8 - 1.0 (m, 6H), 1.2 - 1.4 (m, 8H), 1.45 (m, 2H), 1.8 (m, 2H), 1.9 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 2.9 - 3.0 (m, 5H), 7.0 - 7.1 (m, 3H), 7.2 (t, 1H).

MS (APCI) : M/Z ( $\text{MH}^+$ ) 379.1;  $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 379.2.

#### Example 49

##### 3-Hexyl-6-methyl-6-[3-(2-pyridyl)phenyl]-3-azabicyclo[3.1.0]hexane



20

3-Hexyl-6-methyl-6-[3-(2-pyridinyl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one (Preparation 68, 33 mg, 0.09 mmol) was dissolved in tetrahydrofuran (10 ml) at 0°C. Lithium aluminium hydride (1M in tetrahydrofuran, 0.2 ml, 0.2 mmol) was added under nitrogen and then the reaction mixture was stirred at room temperature for 16h. The reaction

25

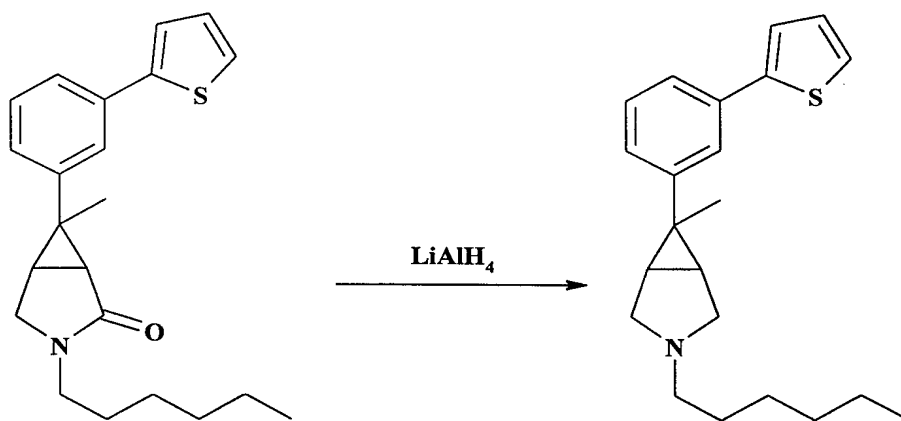
mixture was quenched by adding aqueous sodium hydroxide solution (2N, 0.4 ml), followed by solid sodium hydrogen carbonate and ethyl acetate. The reaction mixture was stirred vigorously and then filtered through Celite®. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel eluting with ethyl acetate to give the product as a colourless oil (13 mg, 41%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.55 - 1.65 (m, 5H), 1.8 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 7.2 - 7.4 (m, 4H), 7.7 - 7.8 (m, 2H), 7.9 (m, 1H), 8.7 (m, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 335.6; C<sub>23</sub>H<sub>30</sub>N<sub>2</sub> + H requires 335.2.

#### Example 50

##### 3-Hexyl-6-methyl-6-[3-(2-thienyl)phenyl]-3-azabicyclo[3.1.0]hexane



3-Hexyl-6-methyl-6-[3-(2-thienyl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one (Preparation 69, 64 mg, 0.19 mmol) was dissolved in tetrahydrofuran (20 ml) at 0°C. Lithium aluminium hydride (1M in tetrahydrofuran, 0.4 ml, 0.4 mmol) was added under nitrogen and then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by adding aqueous sodium hydroxide solution (2N, 0.8 ml), followed by solid sodium hydrogen carbonate and ethyl acetate. The reaction mixture was stirred vigorously and then filtered through Celite®. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel eluting the product with hexane : ethyl acetate (2 : 1) as a colourless oil (66 mg, 64%).



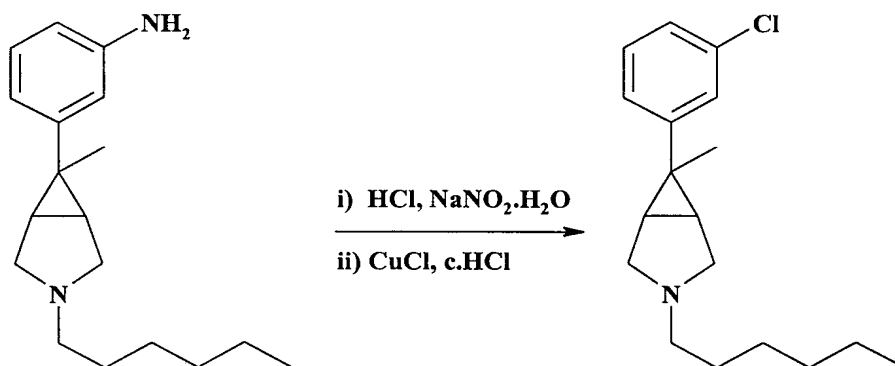
NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.8 (m, 3H), 1.2 - 1.4 (m, 6H), 1.45 (m, 2H), 1.55 (s, 3H), 1.8 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 7.0 (t, 1H), 7.15 (d, 1H), 7.2 - 7.35 (m, 3H), 7.4 (d, 1H), 7.5 (s, 1H).

MS (TSP) : M/Z ( $\text{MH}^+$ ) 340.3;  $\text{C}_{22}\text{H}_{29}\text{NS} + \text{H}$  requires 340.2.

5

### Example 51

#### 6-(3-Chlorophenyl)-3-hexyl-6-methyl-3-azabicyclo[3.1.0]hexane



10

A solution of sodium nitrite (97 mg, 1.4 mmol) dissolved in water (2 ml) was added to 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.17 g, 0.61 mmol) dissolved in aqueous hydrochloric acid (2.0 M, 2 ml) over a few minutes at 0°C. After 30 min at 0°C, the reaction mixture was added to copper (I) chloride (1.57 g, 15.8 mmol) in concentrated hydrochloric acid (4.0 ml). After stirring the reaction mixture at room temperature for 45 min, the reaction mixture was heated to 90°C for 5 min. The reaction mixture was poured cautiously on to solid, pre-wetted sodium hydrogen carbonate and the product was extracted firstly with diethyl ether and then ethyl acetate. The combined organic extracts were dried ( $\text{MgSO}_4$ ) and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with hexane : ethyl acetate (8 : 1) to give the product (69 mg, 39%).

15

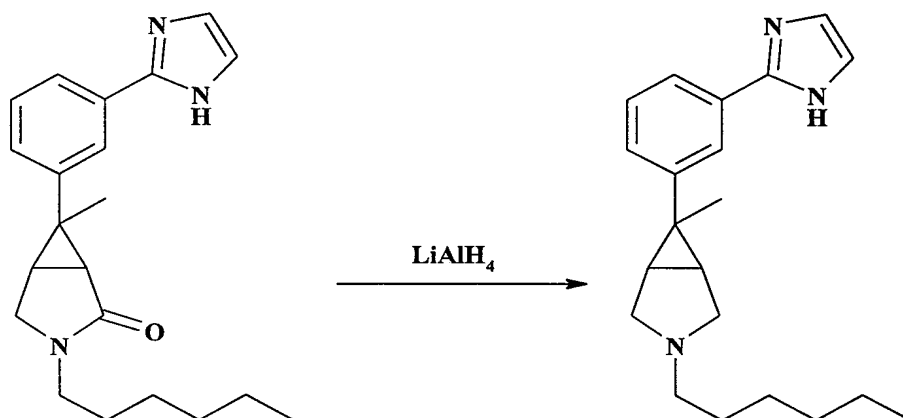
20

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.4 (m, 2H), 1.5 (m, 3H), 1.75 (m, 2H), 2.4 (m, 2H), 2.75 (m, 2H), 2.95 (m, 2H), 7.0 - 7.3 (m, 4H).

MS (TSP) : M/Z ( $\text{MH}^+$ ) 292.2;  $\text{C}_{18}\text{H}_{26}\text{ClN} + \text{H}$  requires 292.2.

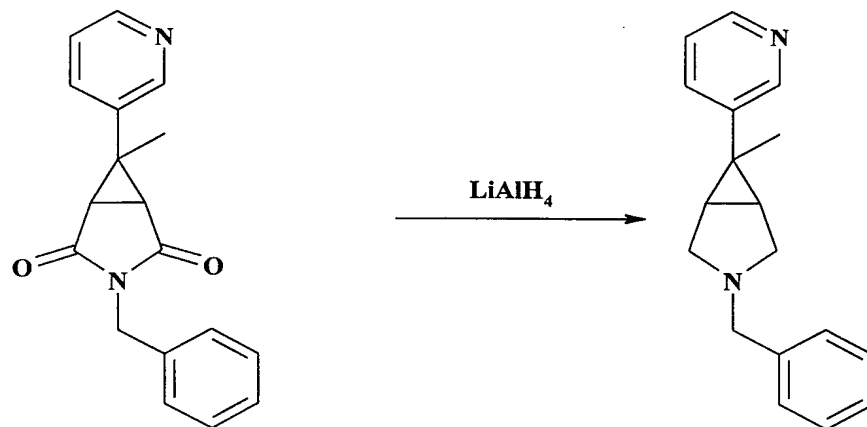
25

### Example 52

3-Hexyl-6-[3-(1*H*-imidazol-5-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]hexane

- 5 To a solution of 3-hexyl-6-[3-(1*H*-imidazol-5-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 75, 21 mg, 62.3  $\mu\text{mol}$ ) in tetrahydrofuran (1.5 ml) at room temperature was added lithium aluminium hydride (1.0 M in tetrahydrofuran, 0.12 ml, 0.12 mmol) over 2 min. The reaction mixture was stirred at room temperature for 30 min and then heated under reflux for 2 h before cooling to room temperature. Aqueous
- 10 sodium hydroxide solution (1 M, a few drops) and excess ethyl acetate were added followed by solid sodium hydrogen carbonate. The reaction mixture was stirred rapidly for 1 h before filtering. The mother liquor was concentrated *in vacuo* and the crude residue was chromatographed on silica gel eluting with ethyl acetate and then ethyl acetate : methanol (80 : 20) to give the product as a colourless semi-solid (15 mg, 75%).
- 15 NMR ( $\text{CDCl}_3$ , selected data for the free base: 0.85 (m, 3H), 1.2 - 1.4 (m, 6H), 1.45 (m, 2H), 1.5 (s, 3H), 1.8 (m, 2H), 2.5 (m, 2H), 2.85 - 3.0 (m, 4H), 7.15 (d, 1H), 7.2 - 7.25 (m, 2H), 7.5 (m, 1H), 7.65 (m, 1H), 7.7 (s, 1H).
- MS (ES) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 324.3;  $\text{C}_{21}\text{H}_{29}\text{N}_3 + \text{H}$  requires 324.2.

20 Example 533-Benzyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane



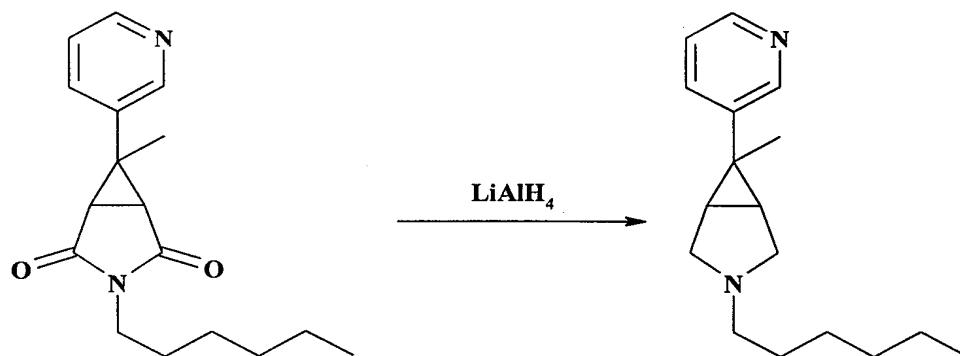
To a solution of 3-benzyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, (Preparation 77, 1.0 g, 3.42 mmol) in tetrahydrofuran (50 ml), was added lithium aluminium hydride (1.0 M in tetrahydrofuran, 13.7 ml, 14.0 mmol). The reaction mixture was heated under reflux for 2 h, cooled to room temperature for 16 h and then refluxed for a further 3 h. The reaction mixture was cooled to room temperature, aqueous sodium hydroxide solution (5M, 14 ml) was added followed by ethyl acetate (20 ml). The reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel, eluting with methanol : dichloromethane : 0.880 ammonia (2 : 97 : 1 and then 5 : 94 : 1) to give the product (0.30 g, 33%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.2 (s, 3H), 1.4 (m, 2H), 2.8 (s, 2H), 3.4 (s, 2H), 4.6 (s, 2H), 7.2 - 7.3 (m, 4H), 7.4 - 7.45 (m, 2H), 7.6 (m, 1H), 8.5 - 8.6 (m, 2H).

MS (TSP) : M/Z (MH<sup>+</sup>) 265.1; C<sub>18</sub>H<sub>20</sub>N<sub>2</sub> + H requires 265.2.

#### Example 54

#### 3-Hexyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane



To a solution of 3-hexyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 78, 0.22 g, 0.78 mmol) in tetrahydrofuran (15 ml) was added lithium  
 5 aluminium hydride (1.0 M in tetrahydrofuran, 1.6 ml, 1.6 mmol). The reaction mixture was heated under reflux for 3 h before cooling to room temperature and stirring for 16 h. Water (2 ml) was added followed by ethyl acetate (5 ml). The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude residue was purified on silica gel eluting with dichloromethane : methanol : 0.880 ammonia (99 : 0 : 1 and then 89  
 10 : 10 : 1) to give the pure product (0.13 g, 64%).

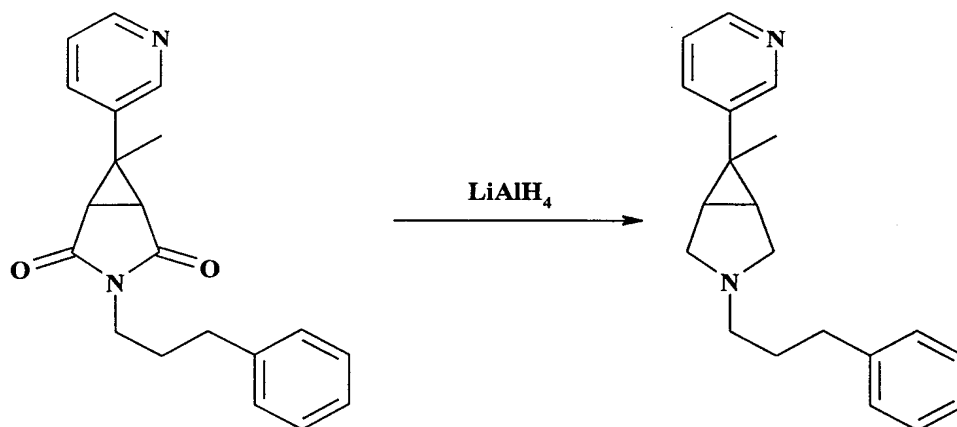
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.5 (m, 2H), 1.55 (s, 3H), 1.8 (m, 2H), 2.5 (m, 2H), 2.85 (m, 2H), 3.05 (m, 2H), 7.15 (m, 1H), 7.55 (m, 1H), 8.4 (m, 1H), 8.55 (m, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 259.9; C<sub>17</sub>H<sub>26</sub>N<sub>2</sub> + H requires 259.2.

15

#### Example 55

#### 6-Methyl-3-(3-phenylpropyl)-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane

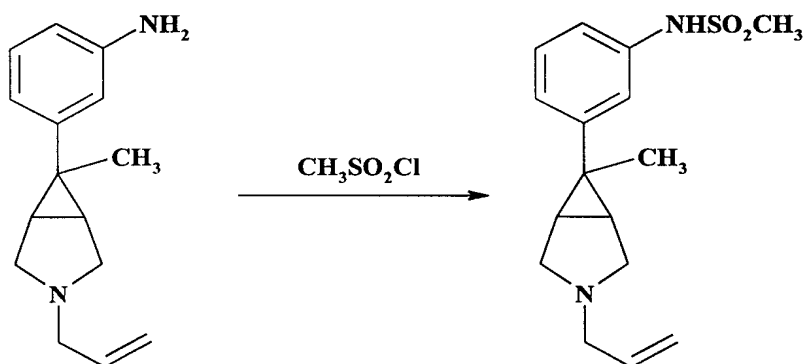


To 6-methyl-3-(3-phenylpropyl)-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 79, 0.23 g, 0.72 mmol) dissolved in tetrahydrofuran (15 ml) was added  
 5 lithium aluminium hydride (1.0 M in tetrahydrofuran, 1.4 ml, 1.4 mmol). The reaction mixture was heated under reflux for 4 h before cooling to room temperature and adding water (2 ml) and ethyl acetate (5 ml). The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude residue was purified on silica gel (10 g) eluting with dichloromethane : methanol : 0.880 ammonia (99 : 0 : 1 and then 89 : 10 : 1) to give the  
 10 pure product (0.2 g, 95%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.6 (s, 3H), 1.75 (m, 4H), 2.45 (m, 2H), 2.65 (m, 2H), 2.8 (m, 2H), 3.1 (m, 2H), 7.05 - 7.3 (m, 6H), 7.5 (m, 1H), 8.4 (m, 1H), 8.5 (s, 1H).  
 MS (TSP) : M/Z ( $\text{MH}^+$ ) 293.0;  $\text{C}_{20}\text{H}_{24}\text{N}_2 + \text{H}$  requires 293.2.

#### 15 Example 56

N-[3-(3-Allyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



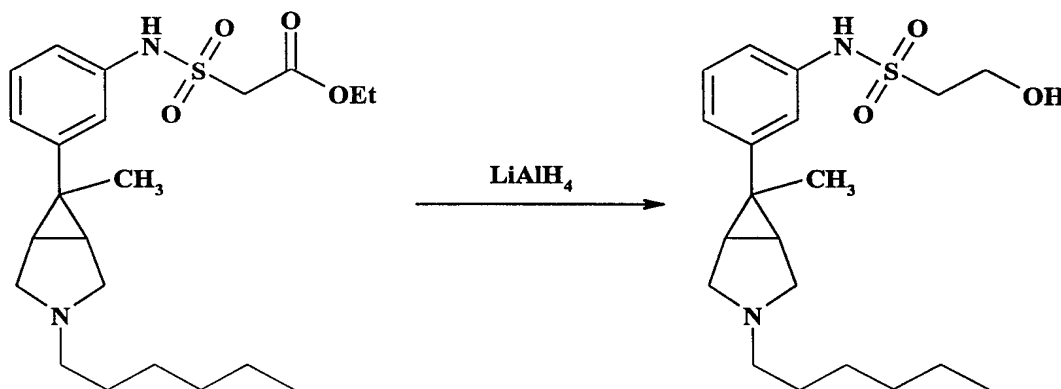
To 3-(3-allyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)aniline (Preparation 52, 8.5 g, 37.2 mmol) dissolved in pyridine (70 ml) at 0°C was added methanesulphonyl chloride (4.32 ml, 55.8 mmol) dropwise over 20 min. The reaction mixture was allowed to stir for 16 h and was then quenched with ice (5 g). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution, followed by water. The organic extracts were concentrated *in vacuo* and then purified by flash chromatography on silica gel, eluting with ethyl acetate : dichloromethane : 2*N* ammonia in methanol (30 : 69 : 1). The product was obtained as a viscous brown oil (7.7 g, 68%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.8 (m, 2H), 2.8 (m, 2H), 2.95 - 3.05 (m, 5H), 3.1 (m, 2H), 5.05 (m, 1H), 5.2 (m, 1H), 5.85 (m, 1H), 7.0 - 7.1 (3H), 7.2 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 307.0; C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 307.1.

#### Example 57

#### N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-2-hydroxy-1-ethanesulfonamide



To a solution of ethyl 2-[[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)anilino]sulfonyl]acetate (Example 41, 0.17 g, 0.43 mmol) in diethyl ether (6.5 ml) was added lithium borohydride (20 mg, 0.91 mmol) followed by methanol (37 l) in diethyl ether (0.5 ml). The reaction mixture was stirred at room temperature for 5 h and then quenched with saturated aqueous sodium hydrogen carbonate solution. The organic

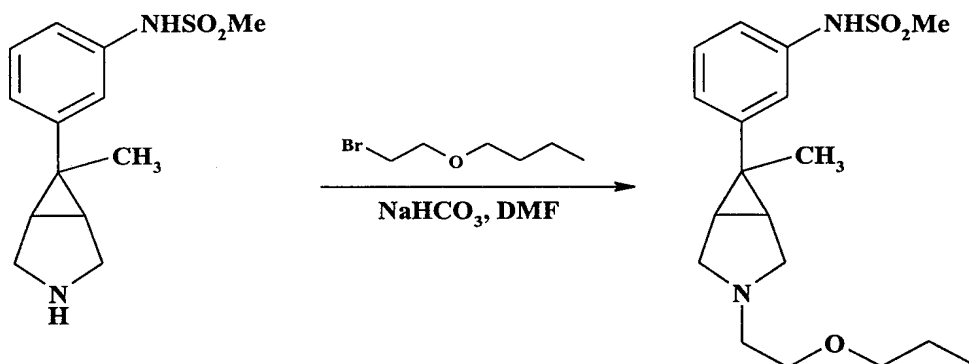
extracts were extracted with ethyl acetate, dried ( $\text{MgSO}_4$ ) and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with ethyl acetate, and then ethyl acetate : methanol : 0.880 ammonia (94 : 5 : 1) to give the product as a colourless oil (10 mg, 6%).

- 5 NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 6H), 1.4 (m, 2H), 1.45 (s, 3H), 1.8 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.2 (m, 2H), 4.1 (m, 2H), 7.0 - 7.15 (m, 3H), 7.2 (m, 1H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 381.1;  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 381.2.

#### 10 Example 58

*N*-{3-[3-(2-Butoxyethyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



15

To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethoxy)butane (38 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (29 mg, 44%).

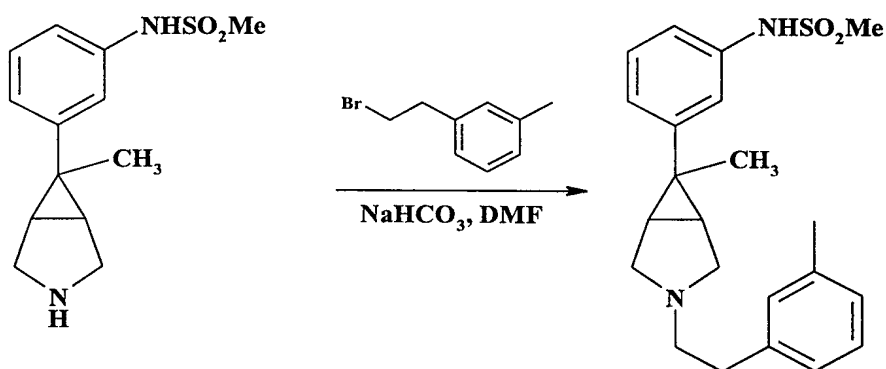
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.95 (t, 3H), 1.35 (m, 2H), 1.45 (s, 3H), 1.55 (m, 2H), 1.75 (m, 2H), 2.7 (m, 2H), 2.9 - 3.05 (m, 7H), 3.45 (m, 2H), 3.5 (m, 2H), 7.0 - 7.15 (m, 3H), 7.25 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 367.1; C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 367.2.

5

### Example 59

N-[3-[6-Methyl-3-(3-methylphenethyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl]methanesulfonamide



10

To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethyl)-3-methylbenzene (A. Mitre, and S. Ghoshe, Ind. J. Chem. Sect. B, 1996, **35B**, 785; 41 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (20 mg, 29%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.45 (s, 3H), 1.8 (m, 2H), 2.35 (s, 3H), 2.7 - 2.8 (m, 4H), 2.85 - 3.1 (m, 7H), 7.0 - 7.3 (m, 8H).

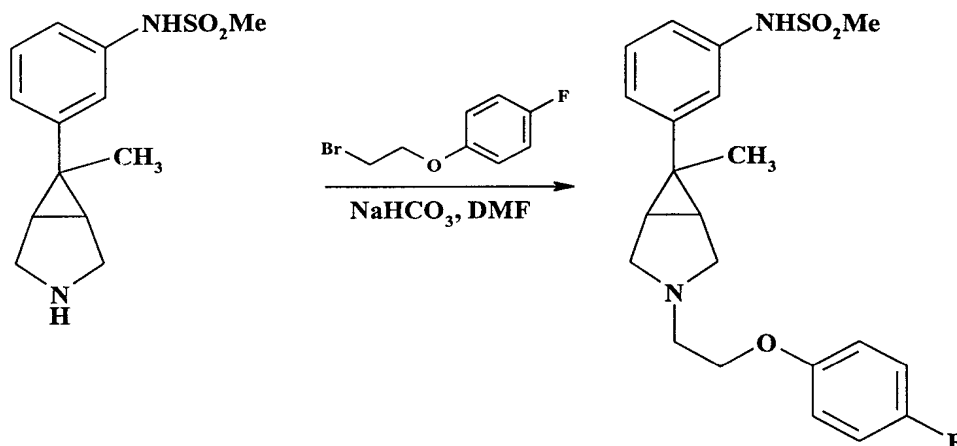
MS (ES) : M/Z (MH<sup>+</sup>) 385.5; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 385.2.

25



Example 60

N-(3-{3-[2-(4-Fluorophenoxy)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 4-fluorophenoxyethyl bromide (45 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (18 mg, 25%).

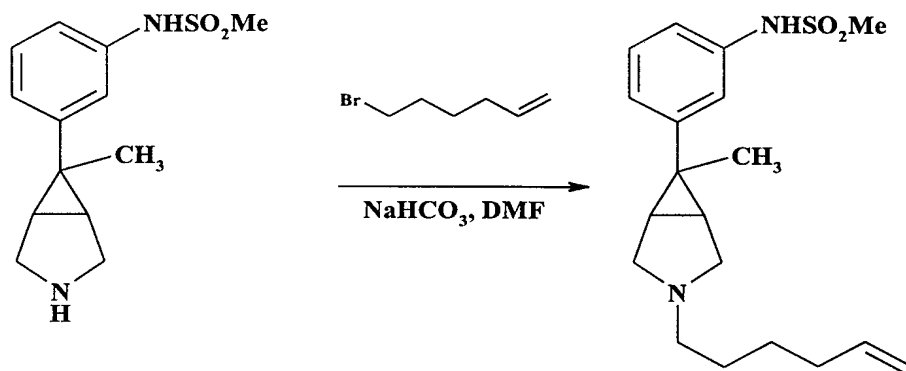
NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.8 (s, 2H), 2.9-3.15 (m, 9H), 4.05 (m, 2H), 6.8 - 6.9 (m, 2H), 6.95 - 7.15 (m, 5H), 7.25 (m, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 405.3; C<sub>21</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>3</sub>S + H requires 405.2.

20

Example 61

N-{3-[3-(5-Hexenyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



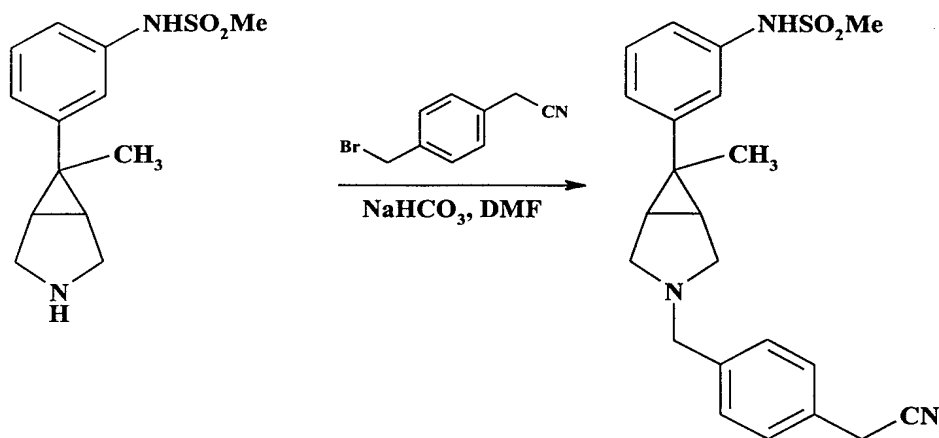
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 6-bromo-1-hexene (34 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (29 mg, 46%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.4 - 1.45 (m, 4H), 1.5 (s, 3H), 1.75 (m, 2H), 2.1 (m, 2H), 2.5 (m, 2H), 2.85 (m, 2H), 2.95 - 3.05 (m, 5H), 4.9 - 5.05 (m, 2H), 5.8 (m, 1H), 7.0 - 7.15 (m, 3H), 7.25 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 349.5; C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 349.2.

#### Example 62

*N*-(3-{3-[4-(Cyanomethyl)benzyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



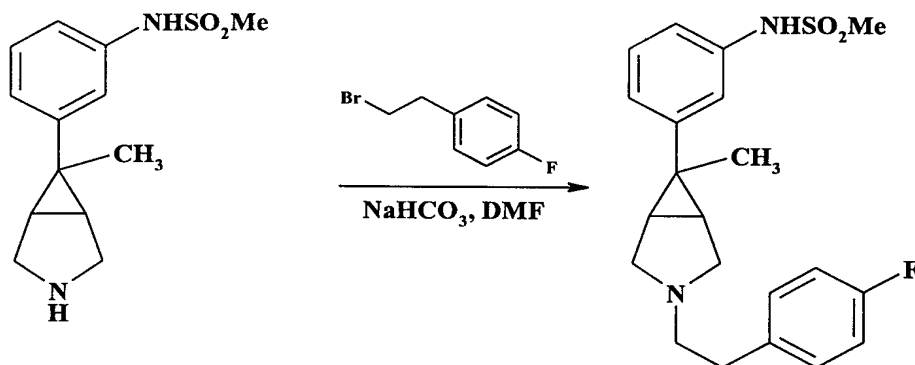
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 2-[4-(bromomethyl)phenyl]acetonitrile (E. Laurent, B. Marquet and R. Tardivel, Tetrahedron, 1991, 47, 3969) (44 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (31 mg, 43%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.6 (s, 3H), 1.80 (m, 2H), 2.85 (m, 2H), 3.0 - 3.1 (m, 5H), 3.7 (s, 2H), 3.75 (s, 2H), 6.75 (br, 1H), 7.0 - 7.1 (m, 3H), 7.2 - 7.4 (m, 5H).

MS (ES) : M/Z (MH<sup>+</sup>) 396.0; C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 396.2.

### Example 63

*N*-{3-[3-(4-Fluorophenethyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



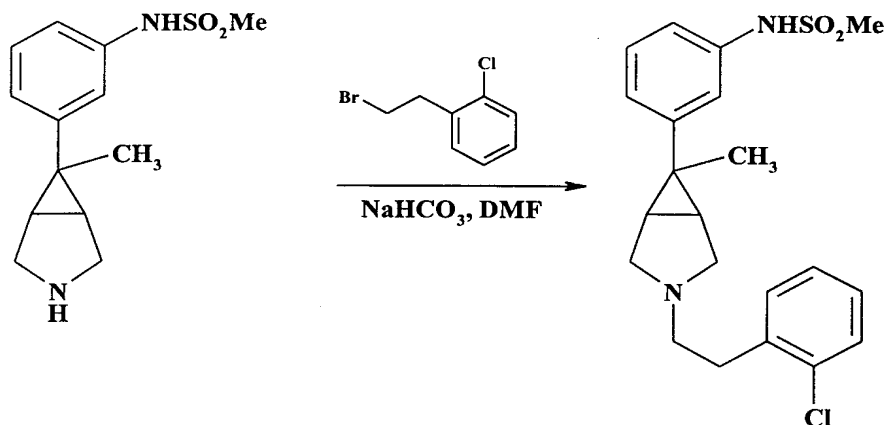
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethyl)-4-fluorobenzene (C. M. Suter, and A. W. Weston, J. Am. Chem. Soc., 1941, 63, 602; 42 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (18 mg, 26%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.65 (s, 3H), 1.8 (m, 2H), 2.75 - 2.85 (m, 4H), 2.9 - 3.1 (m, 7H), 6.9 - 7.3 (m, 8H).

MS (ES) : M/Z (MH<sup>+</sup>) 389.0; C<sub>21</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>2</sub>S + H requires 389.2.

#### Example 64

*N*-{3-[3-(2-Chlorophenethyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



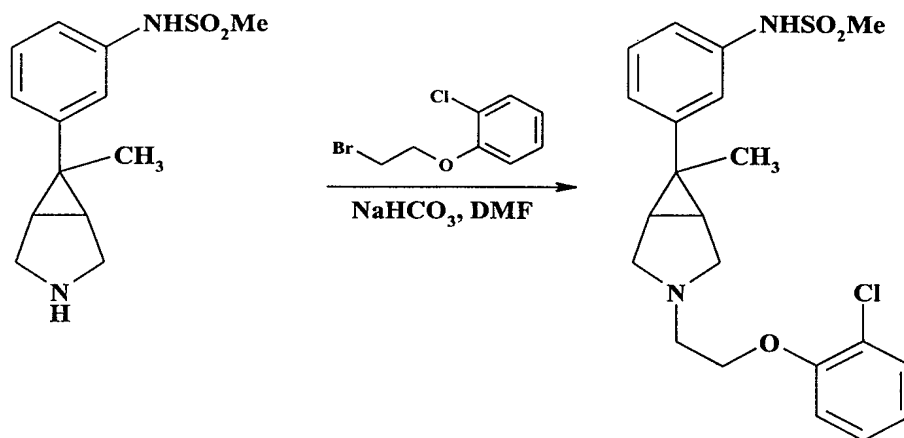
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethyl)-2-chlorobenzene (R. A. Glennon, et al., J. Med. Chem., 1981, 24, 678; 45 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (19 mg, 26%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.45 (s, 3H), 1.8 (m, 2H), 2.75 (m, 2H), 2.85 - 3.1 (m, 9H), 7.0 - 7.4 (m, 8H).

MS (ES): M/Z (MH<sup>+</sup>) 405.0; C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>S + H requires 405.1.

#### Example 65

*N*-(3-{3-[2-(2-Chlorophenoxy)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



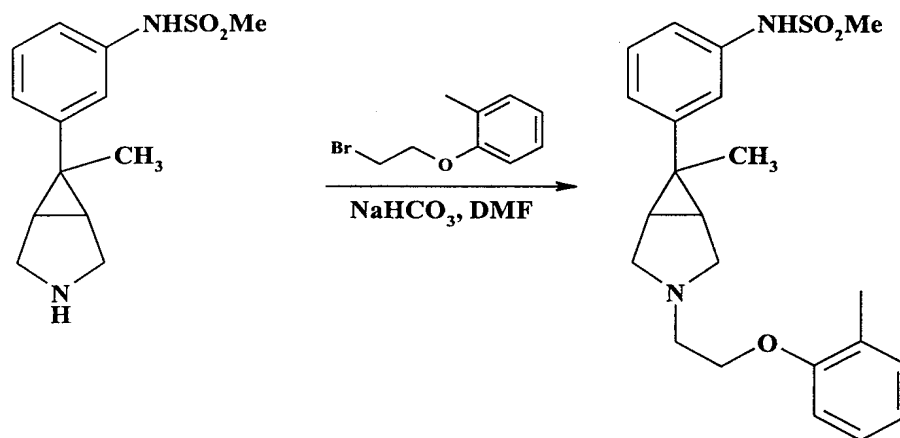
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethoxy)-2-chlorobenzene (J. D. Genzer, C. P. Hutter, and G. C. van Wessem, J. Am. Chem. Soc., 1951, 73, 3159; 49 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (30 mg, 40%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.50 (s, 3H), 1.8 (m, 2H), 3.0 - 3.2 (m, 9H), 4.15 (m, 2H), 6.85 - 6.95 (m, 2H), 7.05 - 7.15 (m, 3H), 7.20 - 7.25 (m, 2H), 7.35 (m, 1H).

MS (ES):  $M/Z$  ( $\text{MH}^+$ ) 421.0;  $\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_3\text{S} + \text{H}$  requires 421.1.

### Example 66

*N*-(3-{6-Methyl-3-[2-(2-methylphenoxy)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



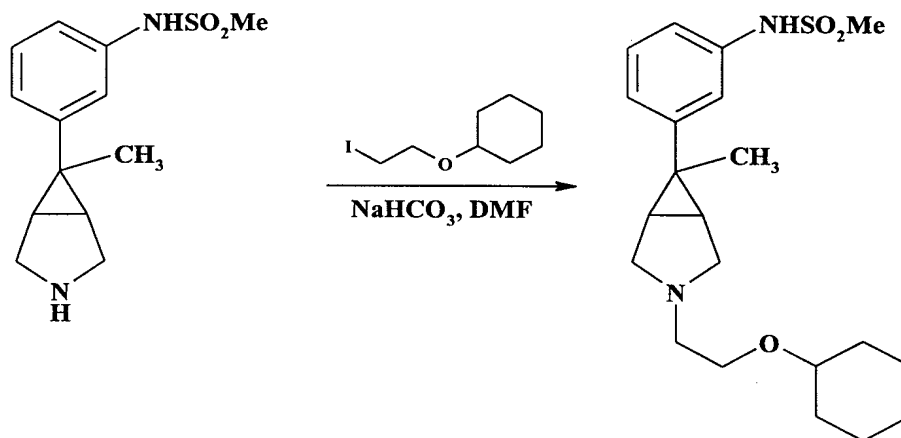
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-bromoethoxy)-2-methylbenzene (45 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (12 mg, 17%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.8 (m, 2H), 2.25 (s, 3H), 2.95 - 3.1 (m, 5H), 3.15 - 3.2 (m, 4H), 4.1 (m, 2H), 6.8 - 6.9 (m, 2H), 7.0 - 7.3 (m, 6H).

MS (ES) : *M/Z* (MH<sup>+</sup>) 401.0; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 401.2.

#### Example 67

*N*-(3-{3-[2-(Cyclohexyloxy)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)-methanesulfonamide



To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(2-iodoethoxy)cyclohexane (Preparation 87, 53 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (33 mg, 47%).

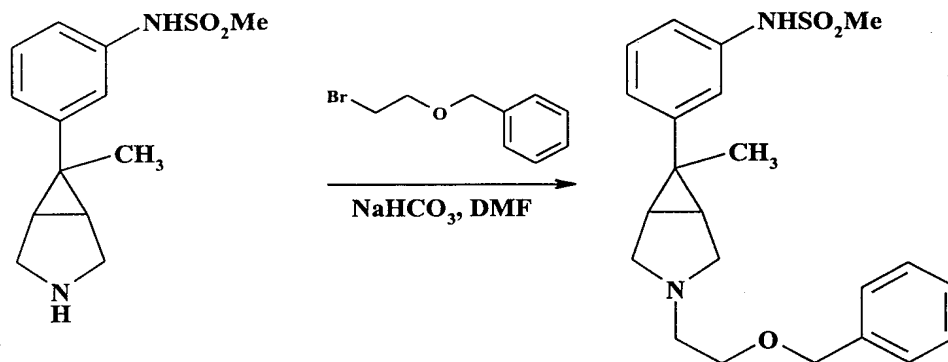
NMR (CDCl<sub>3</sub>, selected data for the free base): 1.15 - 1.35 (m, 5H), 1.45 (s, 3H), 1.5 (m, 1H), 1.65 - 1.8 (m, 4H), 1.9 (m, 2H), 2.7 (m, 2H), 2.9 - 3.1 (m, 7H), 3.25 (m, 1H), 3.55 (m, 2H), 7.0 - 7.15 (m, 3H), 7.25 (t, 1H).

MS (ES): M/Z (MH<sup>+</sup>) 393.1; C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 393.2.

#### Example 68

*N*-(3-{3-[2-(Benzyloxy)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)-methanesulfonamide





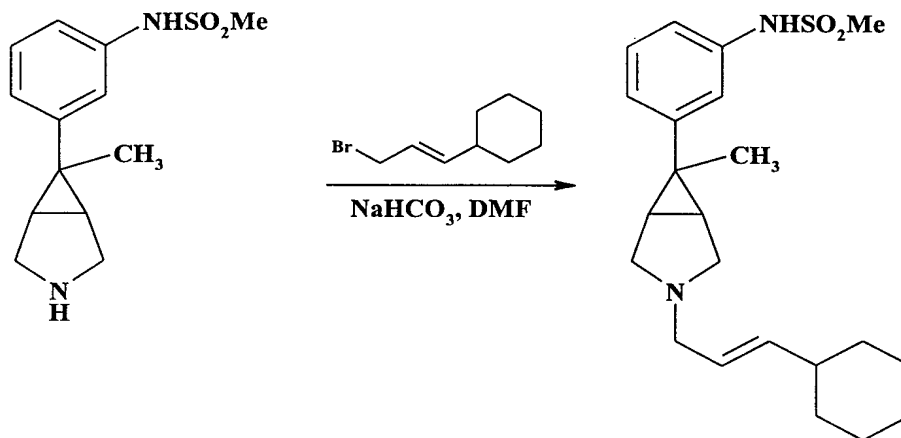
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-[(2-iodoethoxy)methyl]benzene (Preparation 90, 54 mg, 0.20 mmol). The reaction mixture was heated for 15 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (36 mg, 50%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.5 (s, 3H), 1.8 (s, 2H), 2.75 (m, 2H), 2.95 - 3.05 (m, 7H), 3.55 (m, 2H), 4.55 (s, 2H), 7.0 - 7.1 (m, 3H), 7.2 - 7.4 (m, 6H).

MS (ES) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 401.0;  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 401.2.

#### Example 69

*N*-[3-{3-[(*E*)-3-Cyclohexyl-2-propenyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl]methanesulfonamide



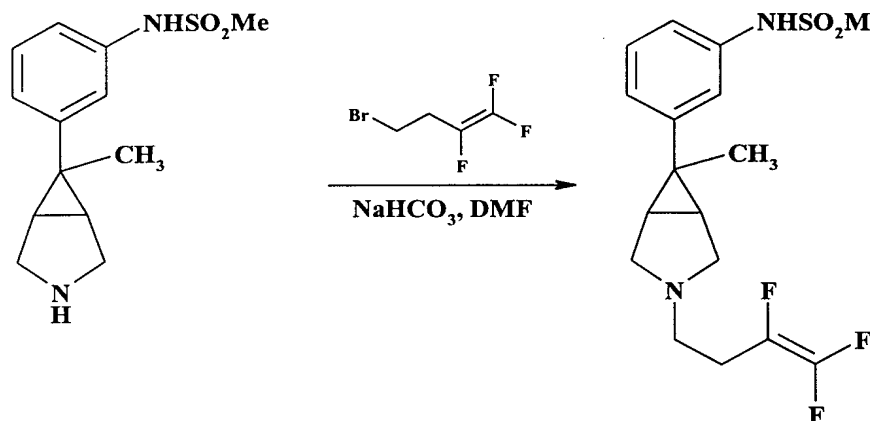
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-[(*E*)-3-bromo-1-propenyl]cyclohexane (Preparation 88, 42 mg, 0.20 mmol). The reaction mixture was heated for 15 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (30 mg, 43%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.0 - 1.35 (m, 6H), 1.5 (s, 3H), 1.6 - 1.75 (m, 4H), 1.8 (m, 2H), 1.95 (m, 1H), 2.85 - 2.95 (m, 4H), 3.0 (s, 3H), 3.1 (m, 2H), 5.4 - 5.6 (m, 2H), 7.0 - 7.15 (m, 3H), 7.15 (dd, 1H).

MS (ES): M/Z (MH<sup>+</sup>) 389.1; C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 389.2.

#### Example 70

*N*-{3-[6-Methyl-3-(3,4,4-trifluoro-3-butenyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



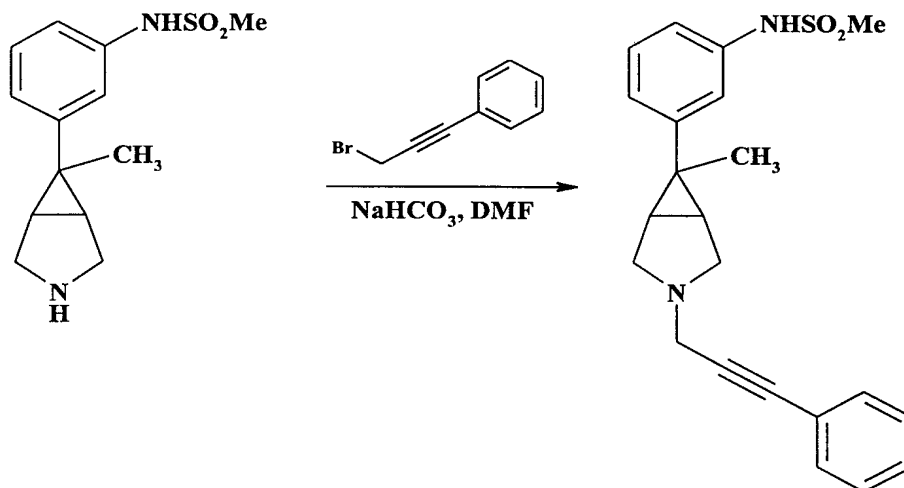
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 4-bromo-1,1,2-trifluorobut-1-ene (39 mg, 0.20 mmol). The reaction mixture was heated for 30 h at 50°C, then further 4-bromo-1,1,2-trifluorobut-1-ene (19 mg, 0.10 mmol) was added and the reaction mixture was heated for a further 13 h. After the reaction had cooled to room temperature, diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (18 mg, 27%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.75 (m, 2H), 2.45 (m, 2H), 2.7 (m, 2H), 2.85 (m, 2H), 3.0 (s, 3H), 3.1 (m, 2H), 6.7 (br, 1H), 7.05 - 7.15 (m, 3H), 7.25 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 375.0; C<sub>17</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 375.1.

## Example 71

*N*-{3-[6-Methyl-3-(3-phenyl-2-propynyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-methanesulfonamide



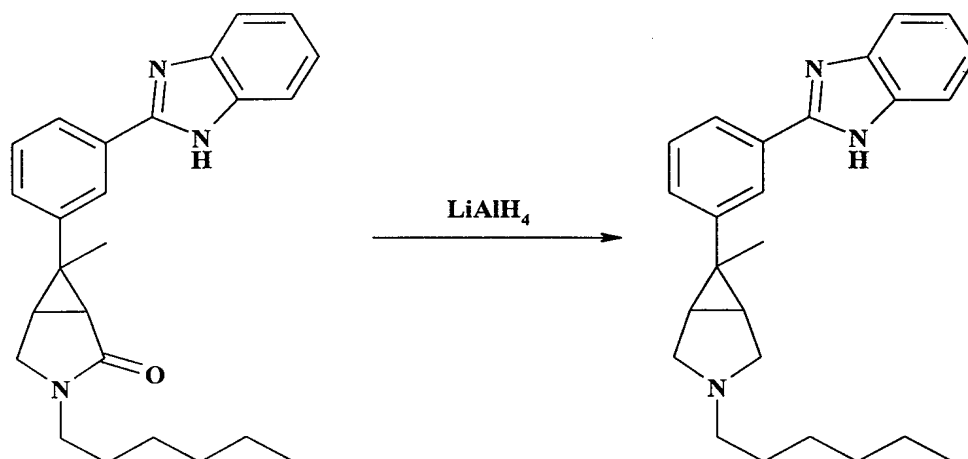
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.18 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (63 mg, 0.75 mmol) and 1-(3-bromo-1-propynyl)benzene (P. Place, C. Vernière and J. Goré, Tetrahedron, 1981, **37**, 1359) (40 mg, 0.20 mmol). The reaction mixture was heated for 15 h at 50°C, and then cooled to room temperature. Diethyl ether (5 ml) was added followed by water (7 ml), the organic extracts were separated and the aqueous layer was washed further with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residues were purified by flash chromatography on an SPE cartridge containing silica gel (5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to give the product as an oil (27 mg, 39%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.55 (s, 3H), 1.8 (m, 2H), 3.0 (s, 3H), 3.1 (m, 2H), 3.2 (m, 2H), 3.65 (s, 2H), 7.0 - 7.15 (m, 3H), 7.2 - 7.35 (m, 4H), 7.4 - 7.45 (m, 2H).

MS (ES) : M/Z (MH<sup>+</sup>) 381.0; C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 381.2.

#### Example 72

2-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1*H*-benzimidazole



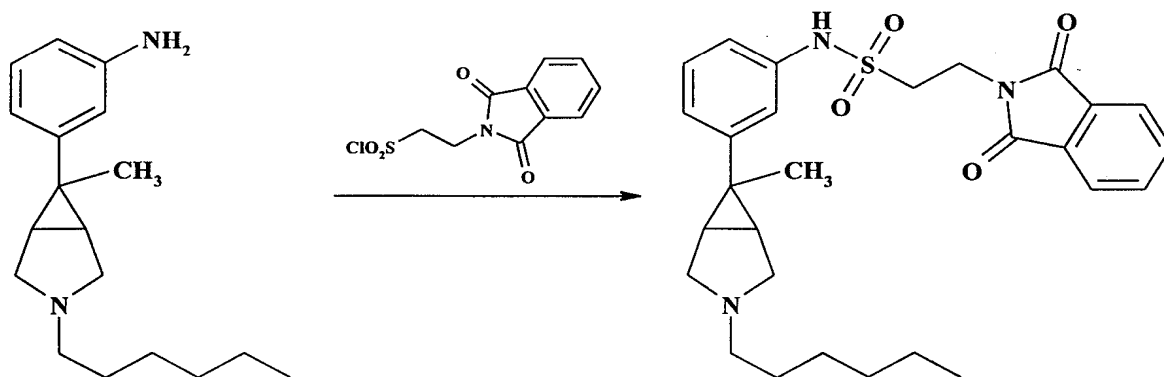
To 6-[3-(1*H*-benzimidazol-2-yl)phenyl]-3-hexyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 81, 61 mg, 1.58 mmol) in tetrahydrofuran (4 ml) stirred under nitrogen was added lithium aluminium hydride (1M in tetrahydrofuran, 0.4 ml, 0.39 mmol) dropwise over several minutes. The reaction mixture was stirred at room temperature for 16 h, further lithium aluminium hydride (1M in tetrahydrofuran, 0.4 ml, 0.39 mmol) was added and the reaction mixture was heated under reflux for 1 h and then cooled to room temperature. The reaction mixture was quenched with aqueous sodium hydroxide solution (2M, 1.0 ml) and excess solid sodium hydrogen carbonate was added followed by ethyl acetate (15 ml). The reaction mixture was stirred rapidly for 30 min, filtered through Celite® and after washing with ethyl acetate (15 ml) the combined organic solution was concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with ethyl acetate and then ethyl acetate : methanol : 0.880 ammonia (90 : 10 : 1) to give the product as a white solid ( 31 mg, 53%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 6H), 1.4 - 1.5 (m, 5H), 1.6 (m, 2H), 2.4 (m, 2H), 2.75 (m, 2H), 2.85 (m, 2H), 7.2 - 7.3 (m, 3H), 7.35 (m, 1H), 7.5 (m, 1H), 7.75 - 7.9 (m, 2H), 8.0 (s, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 374.1; C<sub>25</sub>H<sub>31</sub>N<sub>3</sub> + H requires 374.3.

### Example 73

2-(1,3-Dioxo-1,3-2*H*-isoindol-2-yl)-*N*-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide



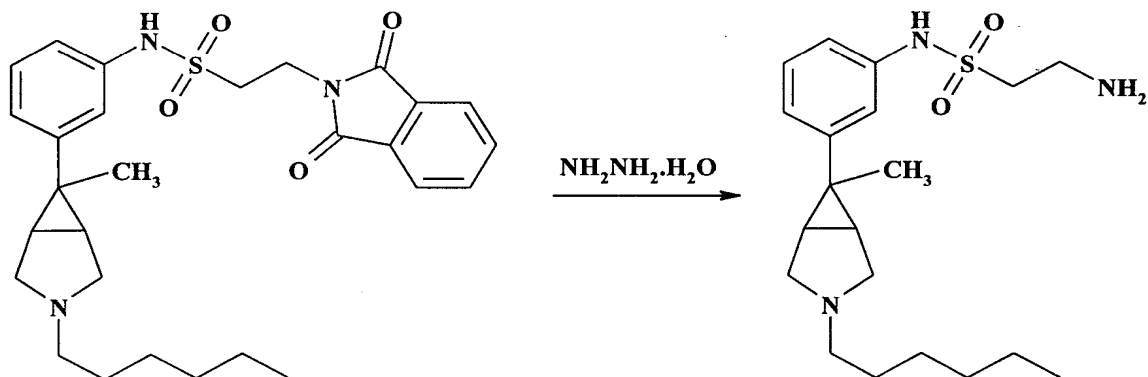
A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (8 ml) stirred under nitrogen was treated with 2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-ethanesulfonyl chloride (0.50 g, 1.84 mmol). The reaction mixture was stirred at room temperature for 16 h and then concentrated *in vacuo*. The crude residue was dissolved in dichloromethane (30 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), the aqueous phase was extracted with dichloromethane (2 x 30 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude dark red gum was triturated with diethyl ether to give the product as a brown powder (80 mg, 42%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 (t, 3H), 1.2 - 1.4 (m, 6H), 1.45 (m, 2H), 1.5 (s, 3H), 1.75 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 2.95 (m, 2H), 3.5 (m, 2H), 4.05 (m, 2H), 7.0 (d, 1H), 7.1 (d, 1H), 7.15 - 7.25 (m, 2H), 7.75 (m, 2H), 7.85 (m, 2H).

MS (ES) : M/Z (MH<sup>+</sup>) 510.1; C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>S + H requires 510.2.

#### Example 74

2-Amino-N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide



A solution of 2-(1,3-dioxo-1,3-2H-isoindol-2-yl)-N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide (Example 73, 0.70 mg, 0.14 mmol) in ethanol (3 ml) was treated with hydrazine monohydrate (6.7  $\mu$ l, 0.4 mmol). The reaction mixture was heated under reflux for 3h, the reaction mixture was cooled and filtered, the white precipitate was washed with ethanol and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5 g) eluting the product with a gradient of methanol : ethyl acetate : 0.88 ammonia solution (10 : 90 : 1 and then 20 : 80 : 1) to give the product as a yellowish gum (50 mg, 94%).

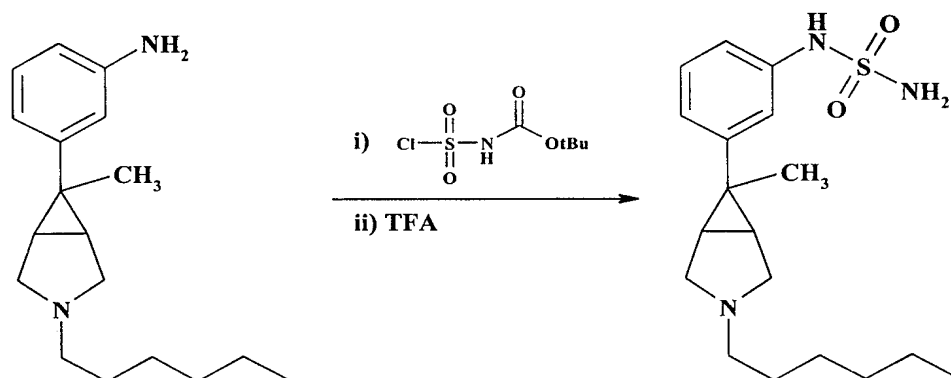
NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.45 (m, 2H), 1.35 (s, 3H), 1.8 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 3.2 (m, 2H), 3.3 (m, 2H), 7.0 - 7.15 (m, 3H), 7.2 (m, 1 H).

MS (TSP): M/Z ( $\text{MH}^+$ ) 380.1;  $\text{C}_{20}\text{H}_{33}\text{N}_3\text{O}_2\text{S} + \text{H}$  requires 380.2.

15

### Example 75

#### N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]sulfamide



A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.25 g, 0.93 mmol) in pyridine (10 ml) stirred under nitrogen was treated at 0°C with [(*tert*-butoxycarbonyl)amino](chloro)dioxo- $\lambda^6$ -sulfane (Preparation 83, 0.24 g, 1.12 mmol).

- 5 The reaction mixture was allowed to warm to room temperature and was stirred overnight before concentrating *in vacuo*. The crude gum was treated with saturated sodium hydrogen carbonate solution (100 ml) and the product was extracted with dichloromethane (3 x 30 ml). The combined organic solution was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give an insoluble off white solid (0.28 g, 0.62 mmol). The white solid was suspended in  
10 dichloromethane (5 ml) cooled to 0°C and treated dropwise with trifluoroacetic acid (1.5 ml). The reaction mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction mixture was poured onto 0.1M aqueous sodium carbonate solution (50 ml) and ice (~50 g). The mixture was stirred for 10 min and then extracted with dichloromethane (3 x 20 ml). The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ) and  
15 concentrated *in vacuo* to give a yellow solid, (130 mg, 60 %).

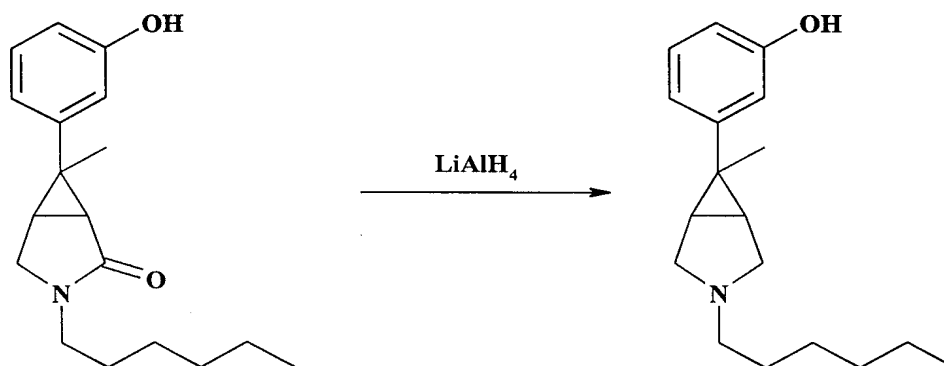
NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.9 (m, 3H), 1.25-1.4 (m, 6H), 1.4 -1.5 (m, 2H), 1.5 (s, 3H), 1.75 (m, 2H), 2.45 (m, 2H), 2.8 (m, 2H), 2.95 (m, 2H), 7.0 -7.1 (m, 3H), 7.25 (m, 1H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 352.1;  $\text{C}_{18}\text{H}_{29}\text{N}_3\text{O}_2\text{S} + \text{H}$  requires 352.2.

20

#### Example 76

#### 3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenol



25



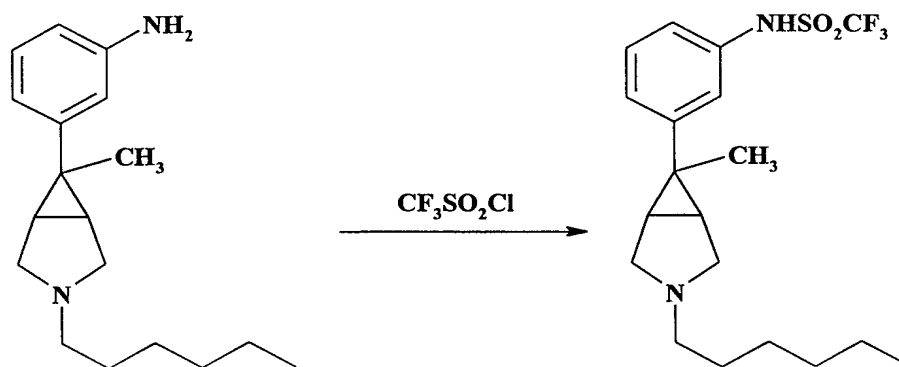
3-Hexyl-6-(3-hydroxyphenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 84, 0.34 g, 1.2 mmol) was dissolved in tetrahydrofuran (10 ml). Lithium aluminium hydride (1M in diethyl ether, 1.5 ml, 1.5 mmol) was added under nitrogen and the reaction mixture was stirred for 1 h, before adding more lithium aluminium hydride (1M in diethyl ether, 3.0 ml, 3.0 mmol) and stirring the reaction mixture for 16 h. The reaction mixture was quenched by the addition of aqueous sodium hydroxide solution (1M, 50 ml) and the product was extracted with dichloromethane (150 ml). The organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give a brown waxy solid. The product was purified by chromatography on silica gel, (20 g) eluting with ethyl acetate to give the pure product as a yellow solid (0.17 g, 51%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 6H), 1.4 (s, 3H), 1.5 (m, 2H), 1.9 (m, 2H), 2.5 (m, 2H), 2.8 (m, 2H), 3.2 (m, 2H), 6.6 - 6.7 (m, 2H), 6.8 (d, 1H), 7.1 (dd, 1H).

MS (ES):  $M/Z$  ( $\text{MH}^+$ ) 274.1;  $\text{C}_{18}\text{H}_{27}\text{NO} + \text{H}$  requires 274.2.

#### Example 77

##### Trifluoro-*N*-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-methanesulfonamide



20

A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (10 ml) cooled at 0°C was treated with trifluoromethanesulphonyl chloride (0.14 g, 0.88 mmol) and 4-dimethylaminopyridine (5 mg). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was poured into saturated aqueous sodium

25

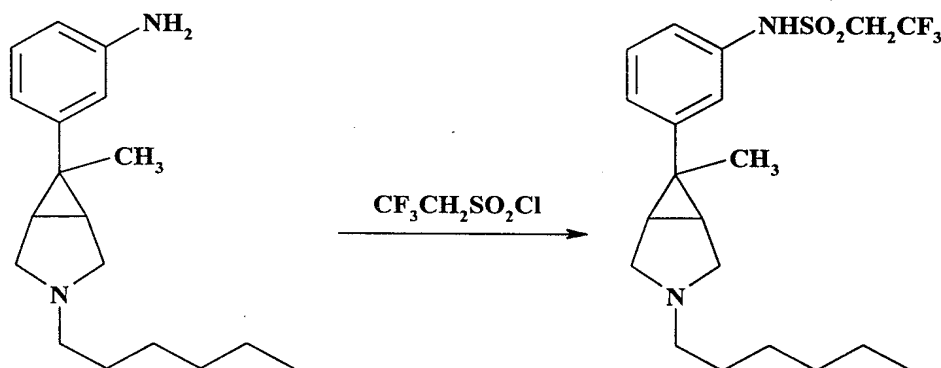
hydrogen carbonate solution (100 ml) and extracted with dichloromethane (3 x 50 ml). The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ) and then concentrated *in vacuo*. The crude residue was purified by preparative HPLC (condition 7) to give a brown solid, (17 mg, 12 %).

- 5 NMR ( $\text{CD}_3\text{OD}$ , selected data for the free base): 0.9 (m, 3H), 1.3 -1.5 (m, 6H), 1.65 (m, 2H), 1.95 (s, 3H), 2.2 (m, 2H), 3.3 - 3.15 (m, 4H), 3.8 (m, 2H), 6.85 (d, 1H), 6.95 (d, 1H), 7.0 (s, 1H), 7.05 (t, 1H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 405.0;  $\text{C}_{19}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 405.2.

10 Example 78

2,2,2-Trifluoro-N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-1-ethanesulfonamide



15

A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.10 g, 0.37 mmol) in pyridine (8 ml) cooled at  $0^\circ\text{C}$  was treated with 2,2,2-trifluoroethanesulphonyl chloride (0.08 g, 0.44 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was poured into saturated aqueous sodium hydrogen carbonate solution (100 ml) and extracted with dichloromethane (3 x 50 ml). The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ) and then concentrated *in vacuo*. The crude residue was purified by preparative HPLC (condition 7) to give a yellow solid, (15 mg, 10 %).

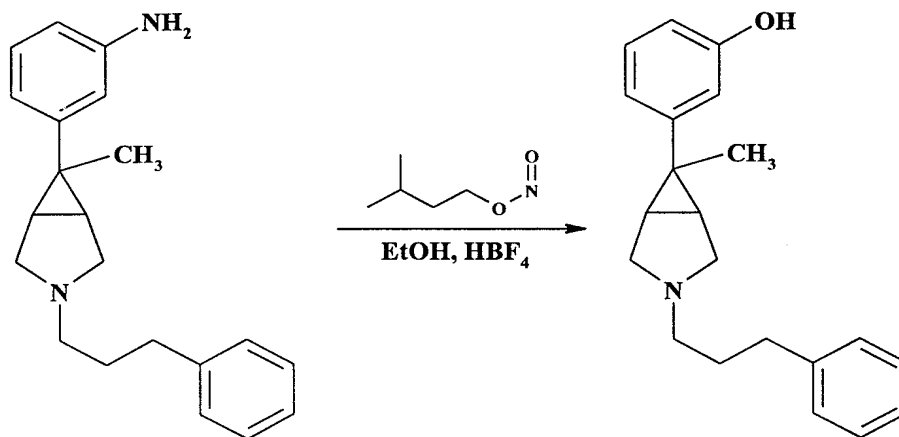
- 20 NMR ( $\text{CD}_3\text{OD}$ , selected data for the free base): 0.9 (m, 3H), 1.2 -1.4 (m, 6H), 1.45 (s, 3H),  
25 1.5 -1.6 (m, 2H), 2.0 (m, 2H), 2.65 (m, 2H), 2.9 (m, 2H), 3.2 (m, 2H), 4.05 (m, 2H), 7.05 - 7.10 (m, 2H), 7.15 (s, 1H), 7.2 - 7.3 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 419.0; C<sub>20</sub>H<sub>29</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 419.2.

### Example 79

#### 3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenol

5



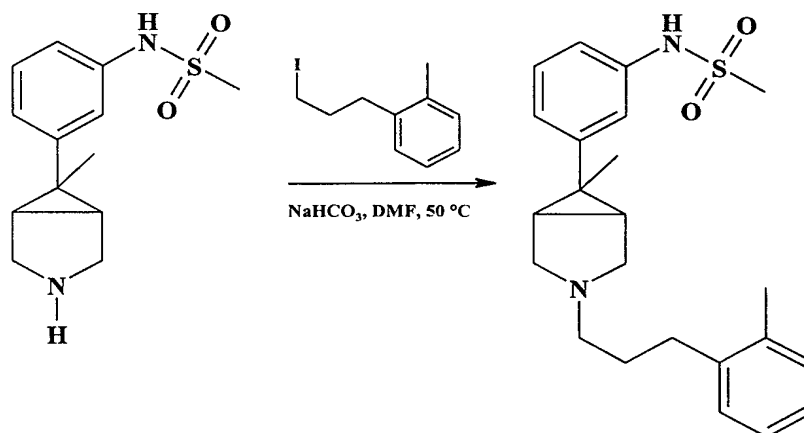
To a stirred solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 100 mg, 0.33 mmol) in absolute ethanol (0.5 ml) at 0°C, was added fluoroboric acid (50% in water, 0.082 ml, 0.66 mmol). The reaction mixture was cooled to -5°C and isoamyl nitrite (0.2 ml, 1.5 mmol) was added over 10 minutes. After stirring the reaction mixture for 30 minutes at -5°C, a red gum had formed. The supernatant solution was removed and concentrated sulphuric acid (1.5 ml) in water (4.5 ml) was added. The reaction mixture was stirred at 50°C for 30 minutes and then at room temperature for 12 h before diluting with water (50 ml) and washing with dichloromethane (25 ml x 3). The aqueous layer was basified to pH 10 with 0.880 ammonia solution and extracted with dichloromethane (3 x 25 ml). The latter organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a yellow oil. This crude residue was purified by chromatography on Florisil™ (5 g) eluting with dichloromethane : methanol: 0.880 ammonia (98 : 1.5 : 0.5) to give a yellow oil (20 mg, 20% yield).

NMR (CDCl<sub>3</sub>, selected data for the free base) 1.45 (s, 3H), 1.75 - 1.85 (m, 4H), 2.50 (m, 2H), 2.65 (m, 2H), 2.85 (m, 2H), 3.10 (m, 2H), 6.6 - 6.7 (m, 2H), 6.80 (d, 1H), 7.10-7.25 (m, 6H).

MS (APCI): M/Z (MH<sup>+</sup>) 307.9, C<sub>21</sub>H<sub>25</sub>NO + H requires 308.2

Example 80

*N*-(3-{6-methyl-3-[3-(3-methylphenyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol) and 1-(3-iodopropyl)-2-methylbenzene (EP279681 A2, 41 mg, 0.16 mmol) and the reaction mixture was heated at 50 °C for 20 h. After cooling, diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak™ cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (23 mg, 30%).

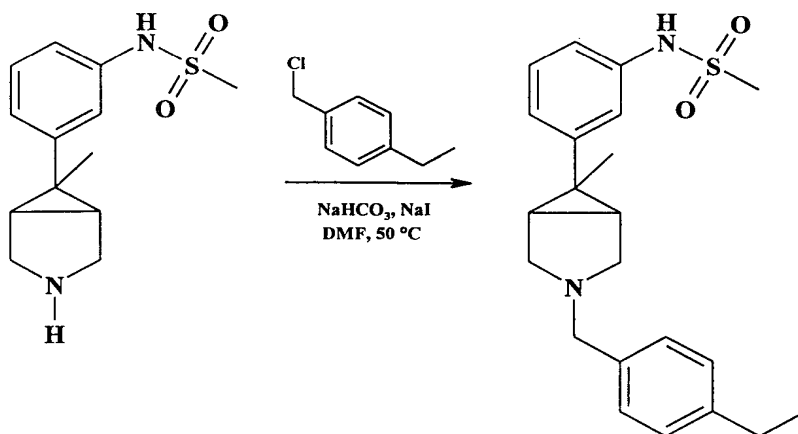
NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.6 (s, 3H), 1.8 (m, 2H), 2.3 (s, 3H), 2.5 (m, 2H), 2.6 (m, 2H), 2.8 (m, 2H), 3.0 (s, 3H), 3.1 (m, 2H), 7.0-7.2 (m, 6H), 7.2-7.3 (m, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 399.1; C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 399.2.

Example 81

*N*-(3-[3-(4-ethylbenzyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl)methanesulfonamide

25



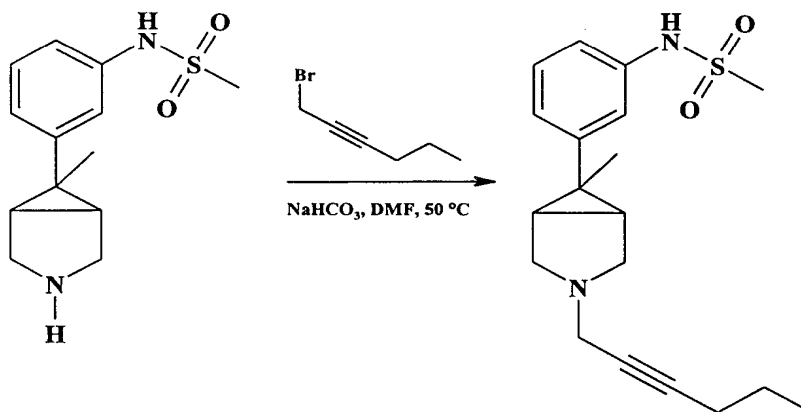
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol), 1-(chloromethyl)-4-ethylbenzene (32 mg, 0.20 mmol) and sodium iodide (catalytic) and the reaction mixture was heated at  $50\text{ }^\circ\text{C}$  for 20 h. After cooling, diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (30 mg, 41%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.2 (t, 3H), 1.6 (s, 3H), 2.6 (q, 2H), 3.0 (s, 3H), 3.1 (m, 2H), 3.6 (m, 2H), 7.0-7.3 (m, 8H).

MS (thermospray) :  $M/Z$  ( $\text{MH}^+$ ) 384.8;  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 385.2.

### Example 82

*N*-(3-{3-[(*E*)-2-hexenyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



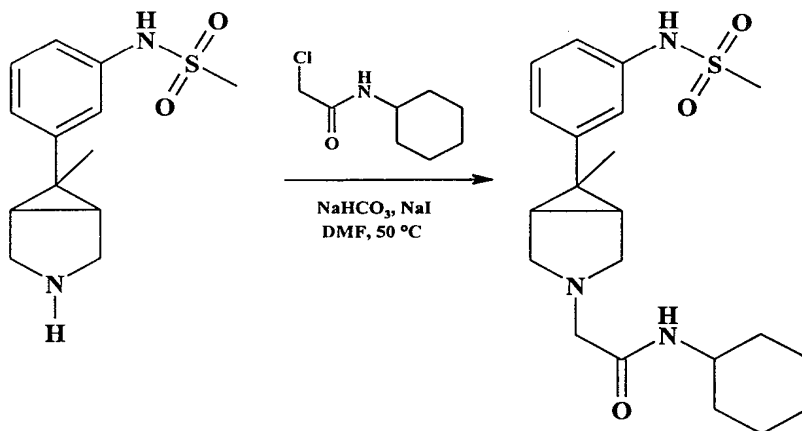
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19 mmol) dissolved in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol) and 1-bromo-2-hexyne (H. A. J. Charles, and R. J. Batten, J. Chem. Soc., Perkin Trans 1, 1987, 1999, 33 mg, 0.2 mmol) and the reaction mixture was heated at  $50^\circ\text{C}$  for 20 h. After cooling diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (33 mg, 50%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.0 (t, 3H), 1.45-1.6 (m, 5H), 1.8 (m, 2H), 2.2 (t, 2H), 2.95-3.1 (m, 7H), 3.4 (m, 2H), 7.0-7.1 (m, 3H), 7.25 (m, 1H).

MS (thermospray) :  $M/Z$  ( $\text{MH}^+$ ) 347.0;  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 347.2.

#### Example 83

*N*-cyclohexyl-2-(6-methyl-6-{3-[(methanesulfonyl)amino]phenyl}-3-azabicyclo[3.1.0]hex-3-yl)acetamide



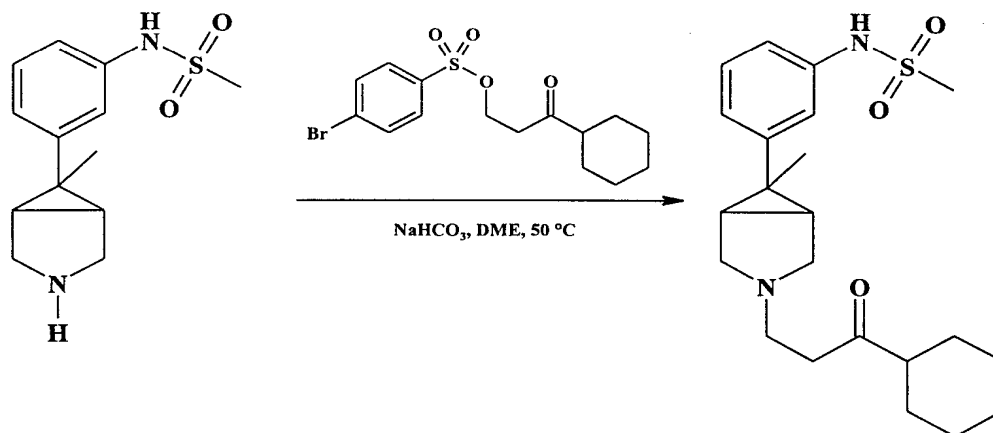
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol), 2-chloro-*N*-cyclohexylacetamide (36 mg, 0.2mmol) and sodium iodide (catalytic) and the reaction was heated at  $50^\circ\text{C}$  for 20 h. After cooling diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (22mg, 28%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.1-1.3 (m, 3H), 1.3-2.0 (m, 12H), 2.9-3.2 (m, 10H), 3.8 (m, 2H), 6.6 (br, 1H), 6.8 (m, 1H), 7.0-7.3 (m, 4H).

MS (electrospray) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 406.1;  $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_3\text{S} + \text{H}$  requires 406.2.

#### Example 84

*N*-{3-[3-(3-cyclohexyl-3-oxopropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19 mmol) in dimethoxyethyl ether (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol), and 3-cyclohexyl-3-oxopropyl-4-bromobenzenesulfonate (Preparation 91, 75 mg, 0.2 mmol) and the reaction mixture was heated at 50 °C for 20 h. After cooling, diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (42 mg, 52%).

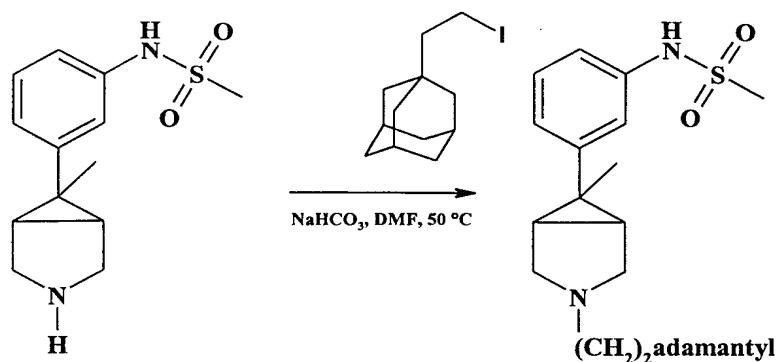
NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.1-1.3 (m, 6H), 1.6-1.9 (m, 10H), 2.3 (m, 1H), 2.6 (t, 2H), 2.7-2.85 (m, 4H), 3.0-3.1 (m, 5H), 7.0-7.15 (m, 3H), 7.2 (m, 1H).

MS (electrospray): M/Z (MH<sup>+</sup>) 405.1; C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 405.2.

### Example 85

*N*-(3-{3-[2-(1-Adamantyl)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide





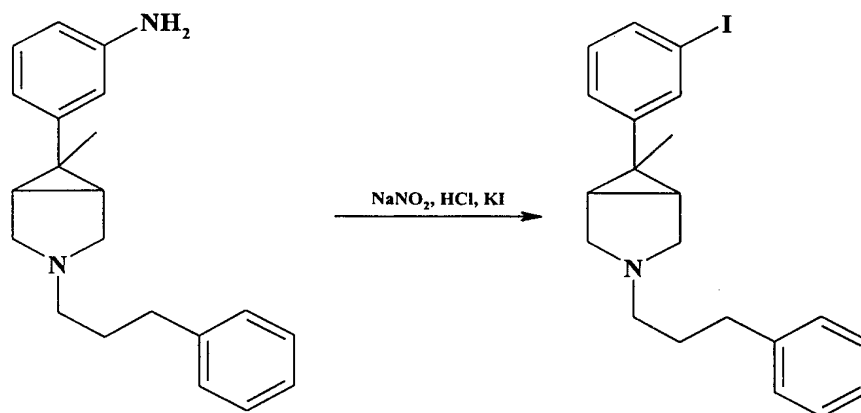
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 57 mg, 0.19 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydrogen carbonate (630 mg, 7.52 mmol) and 1-adamantyl-2-iodoethane (Preparation 93, 58 mg, 0.2 mmol) and the reaction was heated at 50 °C for 20 h. After cooling diethyl ether (5 ml) and water (7 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak™ cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (32 mg, 39%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.2 (m, 3H), 1.5-1.8 (m, 13H), 1.9 (m, 2H), 2.8-2.9 (m, 2H), 3.0 (s, 3H), 7.0-7.3 (m, 4H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 429.2; C<sub>25</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 429.3.

#### Example 86

6-(3-Iodophenyl)-6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane



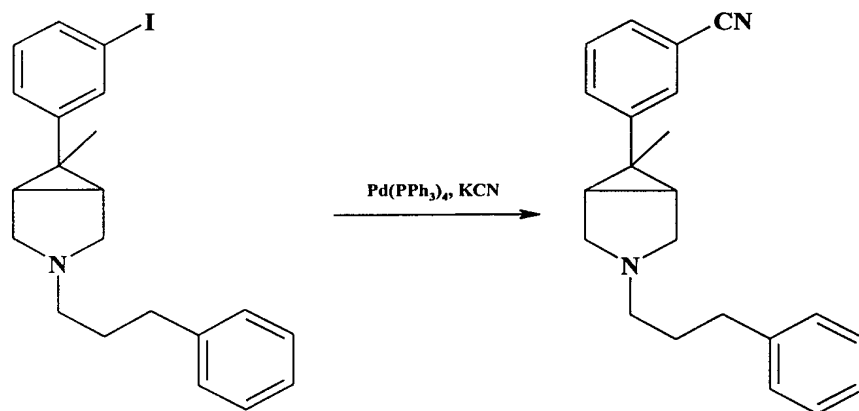
A solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 2.7 g, 8.8 mmol) in hydrochloric acid (2 M, 20 ml) was cooled in an ice bath and treated dropwise with a solution of sodium nitrite (1.3 g, 19 mmol) in water (20 ml). The reaction mixture was stirred for 30 minutes and then a solution of potassium iodide (3.1 g, 19 mmol) in water (20 ml) was added slowly. The reaction mixture was allowed to warm to room temperature over 3 h and then heated at 90°C for 5 minutes, before cooling and slowly pouring onto aqueous saturated sodium hydrogen carbonate (100 ml). The reaction mixture was then extracted with ethyl acetate (4 x 75 ml) and the dark organic extracts were washed with aqueous sodium thiosulphate (10% w/w, 100 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and then concentrated *in vacuo* to give a black oil (1.2 g). The crude residue was purified by chromatography on silica gel (100 g) eluting with hexane : ethyl acetate (70 : 30 and then 30 : 70) to give a black oil (160 mg, 12%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.55 (s, 3H), 1.70-1.85 (m, 4H), 2.50 (t, 2H), 2.65 (t, 2H), 2.80 (m, 2H), 3.05 (m, 2H), 7.00 (m, 1H), 7.05-7.20 (m, 6H), 7.50 (d, 1H), 7.65 (s, 1H).

MS (APCI) : M/Z (MH<sup>+</sup>) 418.0 : C<sub>21</sub>H<sub>24</sub><sup>129</sup>IN + H requires 418.1 .

## 20 Example 87

3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]benzonitrile



To a degassed solution of 6-(3-iodophenyl)-6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane (Example 86, 490 mg, 1.18 mmol) in toluene (20 ml) was added  
 5 *tetrakis*triphenylphosphine palladium (0) (0.68 g, 0.60 mmol) and a finely crushed mixture of potassium cyanide (320 mg, 5.0 mmol) and neutral activated alumina (640 mg) under nitrogen. The reaction mixture was heated to 80°C for 3 h, and then at reflux for 30 minutes before cooling to room temperature and concentrating *in vacuo*. The mixture was absorbed onto silica gel (7 g) and then purified by chromatography on silica gel (100 g)  
 10 eluting with hexane : ethyl acetate (95 : 5 and then 50 : 50) to give a red solid (165mg, 44%).

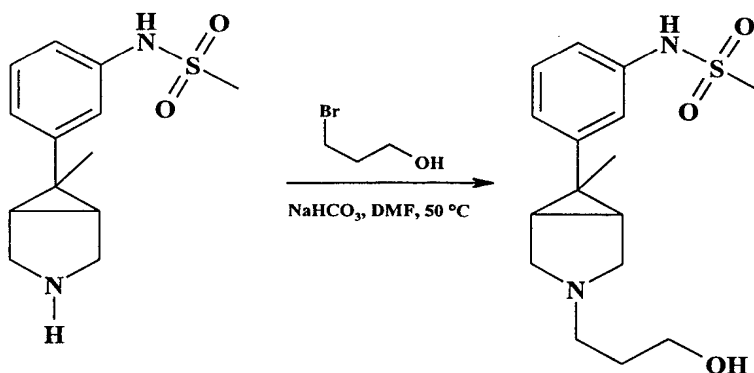
NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.60 (s, 3H), 1.70-1.85 (m, 4H), 2.50 (t, 2H), 2.65 (t, 2H), 2.80 (m, 2H), 3.10 (m, 2H), 7.10-7.60 (m, 9H).

MS (APCI) : M/Z ( $\text{MH}^+$ ) 317.0 :  $\text{C}_{22}\text{H}_{24}\text{N}_2 + \text{H}$  requires 317.2

15

#### Example 88

*N*-{3-[3-(3-hydroxypropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



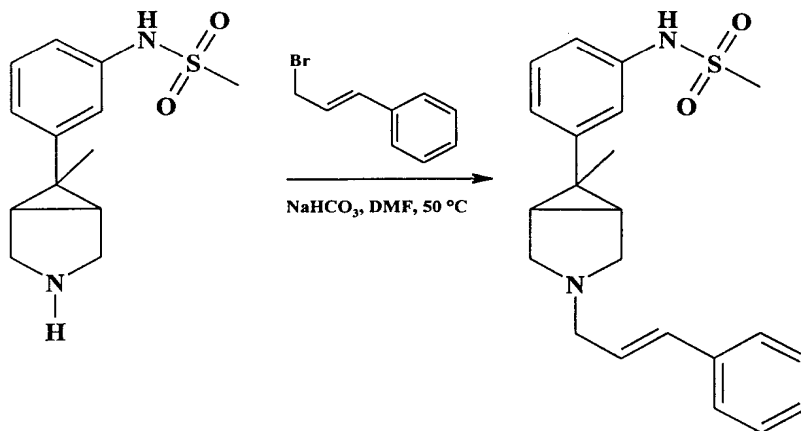
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.89 mmol) in *N,N*-dimethylformamide (8 ml) was added sodium hydrogen carbonate (3 g, 36 mmol) and 3-bromo-1-propanol (0.08 ml, 0.89 mmol), the reaction mixture was heated at 50 °C for 20 h. After cooling, diethyl ether (15 ml) and water (15 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 15 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (42 mg, 15%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.4 (s, 3H), 1.7 (m, 2H), 2.0 (m, 2H), 2.8 (m, 2H), 3.0-3.2 (m, 5H), 3.8 (m, 2H), 7.8-7.1 (m, 3H), 7.3 (m, 1H)

MS (thermospray) : M/Z (MH<sup>+</sup>) 325.1; C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 325.2.

#### Example 89

*N*-(3-{6-methyl-3-[(*E*)-3-phenyl-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



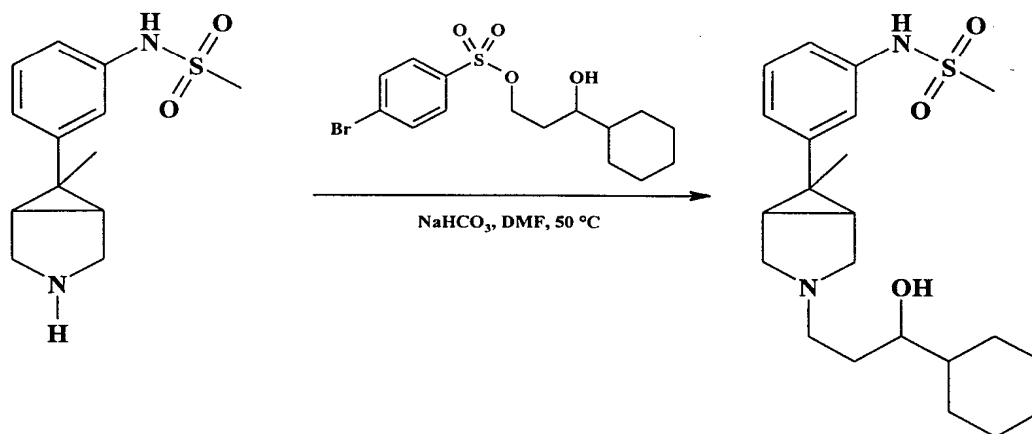
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.89 mmol) in *N,N*-dimethylformamide (8 ml) was added sodium hydrogen carbonate (3 g, 36 mmol) and 1-[(*E*)-3-bromo-1-propenyl]benzene (0.13 ml, 0.89 mmol) and the reaction mixture was heated at  $50^\circ\text{C}$  for 20 h. After cooling, diethyl ether (15 ml) and water (15 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 15 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (40 mg, 12%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.6 (s, 3H), 1.8 (m, 2H), 2.9-3.1 (m, 9H), 3.3 (m, 2H), 6.25 (m, 1H), 6.5 (d, 1H), 7.0-7.1 (m, 7H)

MS (thermospray) :  $M/Z$  ( $\text{MH}^+$ ) 383.3;  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 383.2.

#### Example 90

*N*-{3-[3-(3-Cyclohexyl-3-hydroxypropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



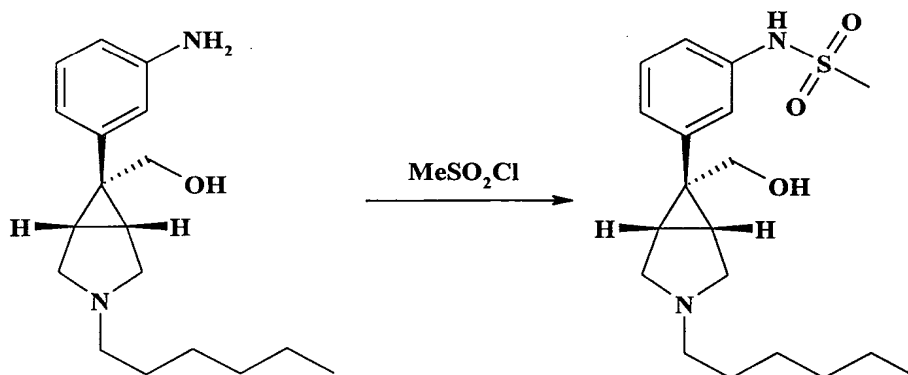
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) in *N,N*-dimethylformamide (8 ml) was added sodium hydrogen carbonate (3 g, 36 mmol) and (S)-3-cyclohexyl-3-hydroxypropyl 4-bromobenzenesulfonate (J. A. Werner *et al*, J. Org. Chem., 1996, 61, 587) (0.08 ml, 0.89 mmol) and the reaction mixture was heated at  $50^\circ\text{C}$  for 20 h. After cooling, diethyl ether (15 ml) and water (15 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 15 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil (90 mg, 25%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 0.9-1.1 (m, 2H), 1.2-1.4 (m, 6H), 1.5 (m, 2H), 1.6-1.8 (m, 6H), 1.9-2.0 (m, 1H), 2.65-2.95 (m, 4H), 3.0 (s, 2H), 3.0-3.2 (dd, 2H), 3.5 (q, 1H), 3.7 (q, 1H), 7.0 (m, 3H), 7.3 (m, 1H)

MS (thermospray) :  $M/Z$  ( $\text{MH}^+$ ) 407.0  $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 407.2.

#### Example 91

*Exo-N*-{3-[3-hexyl-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



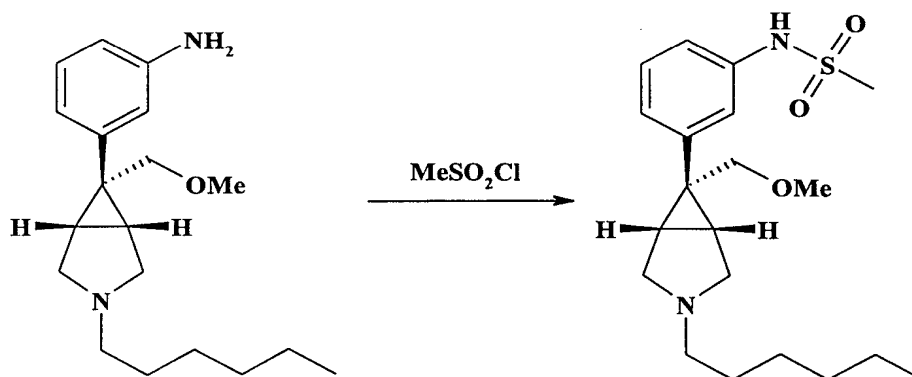
To a solution of [6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methanol (Preparation 94, 15 mg, 0.052 mmol) in anhydrous pyridine (0.2 ml) at 0°C under nitrogen  
 5 was added methanesulfonyl chloride (4.3  $\mu$ l, 6.3 mg, 55  $\mu$ mol) freshly distilled over phosphorous pentoxide. The reaction was stirred for 2 h and gradually allowed to warm to room temperature. The mixture was poured into aqueous sodium hydroxide (1N, 5 ml) and diluted with water (20 ml). The aqueous phase was extracted with ethyl acetate (2 x 25 ml) and the combined organic layers were washed with brine (25 ml). The combined organic  
 10 extracts were dried ( $\text{MgSO}_4$ ) and then concentrated *in vacuo*. The crude product was chromatographed on Merck 230-400 mesh silica gel (5 g) eluting with ethyl acetate : 2M ammonia in ethanol (98 : 2) to give the desired compound as a pale yellow oil (5 mg, 26%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.20 - 1.35 (m, 6H), 1.45 (m, 2H), 1.85 (br s, 2H), 2.50 (t, 2H), 2.65 (br d, 2H), 3.00 (s, 3H), 3.40 (d, 2H), 4.10 (s, 2H),  
 15 7.00 - 7.20 (m, 4H).

MS (Thermospray) : M/Z ( $\text{MH}^+$ ) 366.9;  $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 367.2

### Example 92

20 Exo-N-{3-[3-hexyl-6-(methoxymethyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



To a solution of 3-[3-hexyl-6-(methoxymethyl)-3-azabicyclo[3.1.0]hex-6-yl]aniline (Preparation 98, 11 mg, 0.036 mmol) in anhydrous pyridine (0.3 ml) at 0°C under nitrogen  
 5 was added methanesulfonyl chloride (3.4  $\mu$ l, 5 mg, 43  $\mu$ mol) freshly distilled from phosphorous pentoxide. The reaction was stirred for 3 h and quenched by the addition of water (5 ml) and saturated sodium carbonate solution (25 ml). The aqueous layer was extracted with ethyl acetate (2 x 25 ml) and the organic extracts were washed with brine (25 ml). The organic layers were dried (MgSO<sub>4</sub>) and then concentrated *in vacuo*. The crude  
 10 product was chromatographed on Merck 230-400 mesh silica gel (5 g) eluting with ethyl acetate : 2M ammonia in ethanol (99 : 1) to give the desired product as a pale yellow oil (11 mg, 79%).

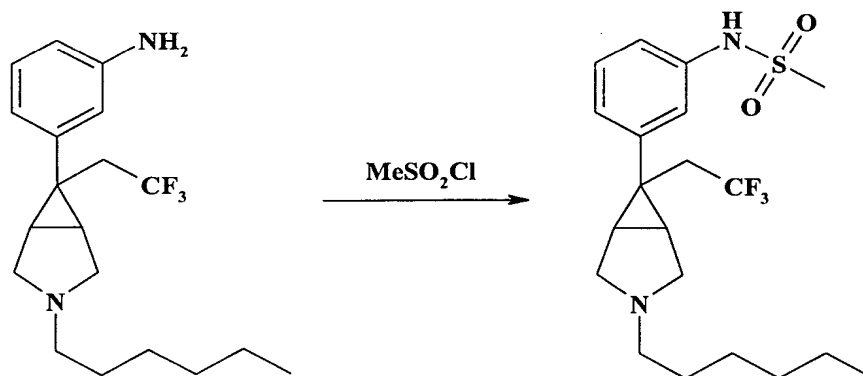
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.90 (m, 3H), 1.15 - 1.45 (m, 8H), 1.80 (br s, 2H), 2.40 (t, 2H), 2.70 (br d, 2H), 3.00 (s, 3H), 3.20 (d, 2H), 3.30 (s, 3H), 4.10 (s, 2H), 7.00  
 15 (d, 1H), 7.10 - 7.20 (m, 2H), 7.25 (m, 1H).

MS (Thermospray) : M/Z (M<sup>+</sup>) 380.6; C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S requires 380.6

### Example 93

N-{3-[3-Hexyl-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methane  
 20 sulfonamide





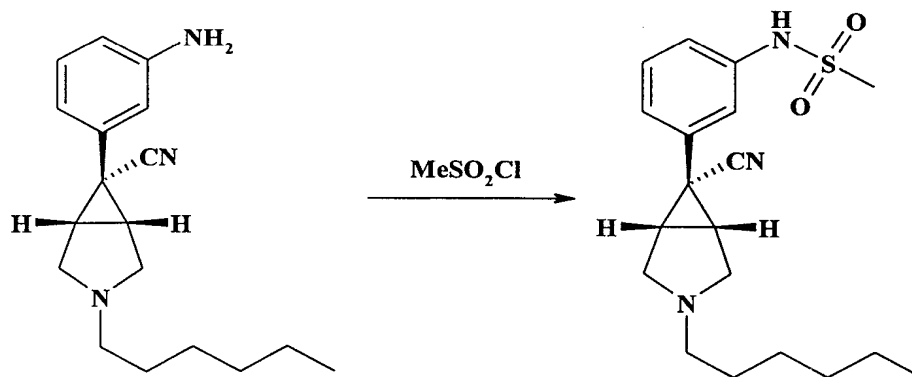
3-[3-Hexyl-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hex-6-yl] aniline (Preparation 101, 143 mg, 0.42 mmol) was dissolved in anhydrous dichloromethane (3 ml) in a dry, nitrogen-flushed flask and cooled to -12°C in an ice/methanol bath. Pyridine (54 µl, 0.67 mmol) was added dropwise followed by methanesulfonyl chloride (39 µl, 0.50 mmol). The mixture was allowed to slowly warm to room temperature, whereupon its colour changed from yellow to bright amber. After 3h, the mixture was treated with water (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO<sub>4</sub>), filtered and the solvent removed *in vacuo*. The crude product was purified by chromatography on silica gel (5g), eluting with hexane : ether (2 : 1) to give the product as an amber gum (71 mg, 40%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85-0.95 (m, 3H), 1.20-1.35 (m, 6H), 1.35-1.45 (m, 2H), 1.85 (m, 2H), 2.40 (t, 2H), 2.60 (d, 2H), 2.95 (s, 3H), 3.15 (q, 2H), 2.25 (d, 2H), 7.05, (d, 1H), 7.10 (d, 1H), 7.20 (s, 1H), 7.25 (s, 1H).

MS (Thermospray): (MH<sup>+</sup>) 419.4, C<sub>20</sub>H<sub>29</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 419.5.

#### Example 94

Exo-N-[3-(6-cyano-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]-methanesulfonamide



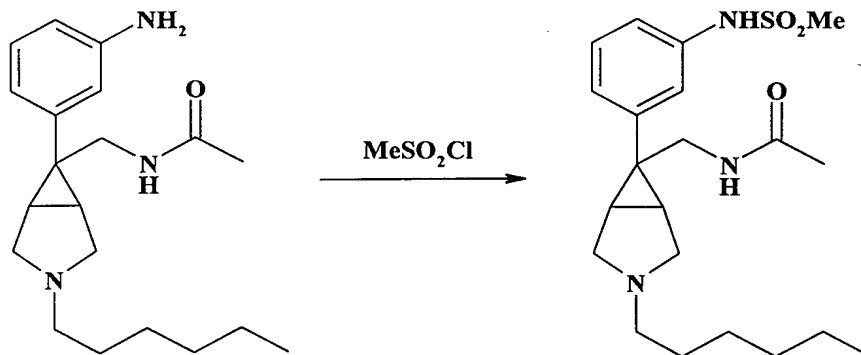
To a solution of 6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile (Preparation 105, 1.7 mg, 6.0  $\mu\text{mol}$ ) in anhydrous pyridine (0.2 ml) at 0°C under nitrogen  
 5 was added methanesulfonyl chloride (0.5  $\mu\text{l}$ , 0.8 mg, 6.6  $\mu\text{mol}$ ) which had been freshly distilled over phosphorous pentoxide. The reaction was stirred for 2 h and gradually allowed to warm to room temperature. The mixture was poured into saturated sodium carbonate solution (5 ml) and diluted with water (20 ml). The aqueous phase was extracted with ethyl acetate (2 x 25 ml) and the organic extracts were washed with brine (25 ml). The  
 10 combined organic extracts were dried ( $\text{MgSO}_4$ ) and then concentrated *in vacuo*. The crude product was chromatographed on Merck 230-400 mesh silica gel (5 g) eluting with ethyl acetate : hexane : 2M ammonia in ethanol (50 : 49 : 1) to give the desired compound as a pale yellow oil (2 mg, 92%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.20 - 1.35 (m, 6H), 1.50 (m,  
 15 2H), 2.20 (m, 2H), 2.50 (m, 2H), 2.85 (m, 2H), 3.00 (s, 3H), 3.30 (m, 2H), 7.10 - 7.30 (m, 4H).

MS (Thermospray) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 362.1;  $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_2\text{S} + \text{H}$  requires 362.2

## 20 Example 95

N-[3-Hexyl-6-{3-[(methanesulphonyl)amino]phenyl}-3-azabicyclo[3.1.0]hex-6-yl)methyl]acetamide



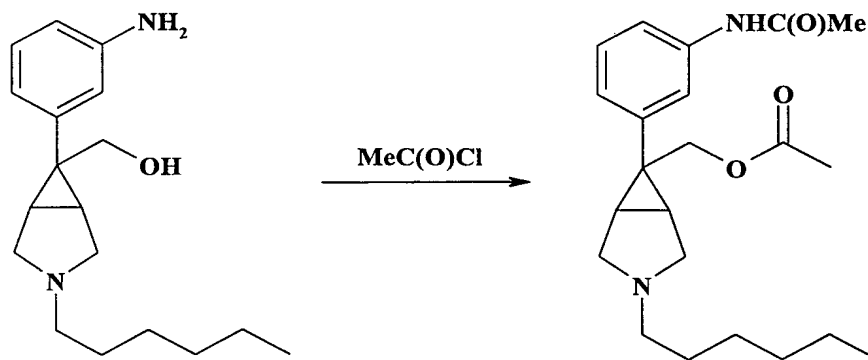
A solution of *N*-[[6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methyl]acetamide (Preparation 108, 67mg, 0.203mmol) in dry pyridine (0.5 ml) was stirred under nitrogen and cooled in an ice bath. Methanesulfonyl chloride (0.02 ml, 0.258 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature with stirring over 16 h. The mixture was then diluted with dichloromethane (5 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (5 ml). The aqueous phase was washed with dichloromethane (2 x 5 ml) and the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an orange residue (80mg). Purification was effected by column chromatography on silica gel (4g) eluting with dichloromethane : ethanol : 0.88 ammonia (200:8:1 and then 150:8:1) to give the title compound as a cream foam (65mg, 78%).

NMR (CDCl<sub>3</sub>): 0.90 (m, 3H), 1.20-1.35 (m, 6H), 1.45 (m, 2H), 1.85 (m, 2H), 1.90 (s, 3H), 2.45 (m, 2H), 2.75 (m, 2H), 3.00 (s, 3H), 3.20 (m, 2H), 4.00 (m, 2H), 5.65 (m, 1H), 7.00-7.10 (m, 2H), 7.20-7.30 (m, 2H).

MS (thermospray): M/Z (MH<sup>+</sup>) 408.4; C<sub>21</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 408.2.

#### Example 96

{6-[3-(Acetylamino)phenyl]-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl}methyl acetate



A solution of [6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methanol (Preparation 94, 0.03 g, 0.09 mmol) in tetrahydrofuran (2 ml), stirred under nitrogen and cooled to 0°C, was treated with triethylamine (0.03 ml, 0.19 mmol) and acetyl chloride (0.01 ml, 0.17 mmol). The reaction mixture was stirred at room temperature for 3 h, saturated aqueous sodium hydrogen carbonate (50 ml) was added and the product was extracted with ethyl acetate (25 ml x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and then concentrated *in vacuo*. The crude residue was purified on a Sep-Pak™ cartridge packed with silica gel (5 g) to give the product as a clear glass, (11 mg, 34 %).

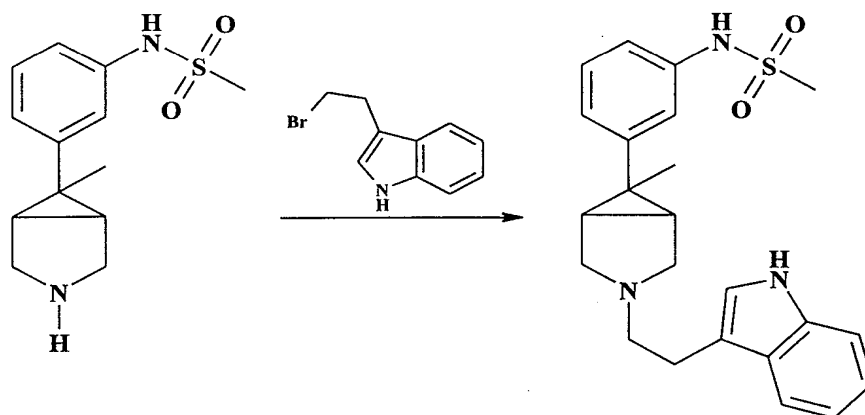
NMR (CDCl<sub>3</sub>, selected data for the free base) : 0.90 (m, 3H), 1.20-1.35 (m, 6H), 1.40 (m, 2H), 1.85 (s, 2H), 1.95 (s, 3H), 2.40 (t, 2H), 2.65 (m, 2H), 3.20 (m, 2H), 4.80 (s, 2H), 7.05 (m, 1H), 7.15-7.30 (m, 2H), 7.45 (s, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 373.3; C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub> + H requires 373.2.

15

**Example 97**

N-(3-{3-[2-(1H-Indol-3-yl)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



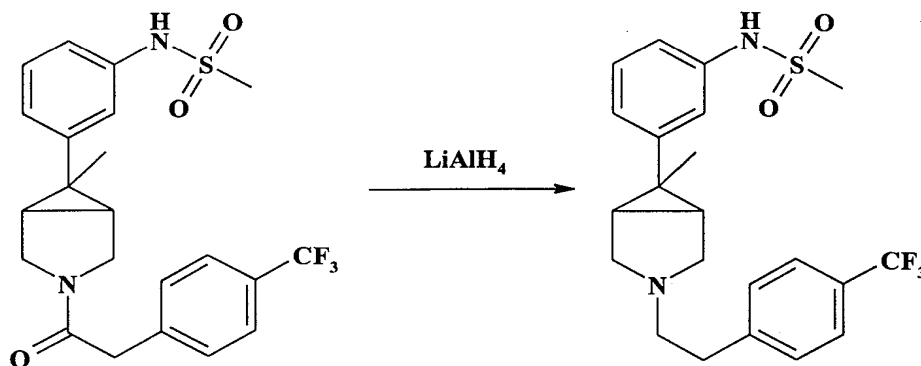
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 50 mg, 0.165 mmol) in *N,N*-  
 5 dimethylformamide (2 ml) was added sodium hydrogen carbonate (35 mg, 0.413 mmol) and 3-(2-bromoethyl)indole (37 mg, 0.165 mmol). The reaction mixture was heated at 55°C for 48 h, cooled to room temperature and concentrated *in vacuo*. Water (10 ml) was added and the product was extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a brown oil. The  
 10 crude product was purified by chromatography using a Biotage Flash 12™ cartridge packed with silica gel (8 g), eluting with hexane : ethyl acetate (100 : 0 and then 0 : 100). The title compound was obtained as a glass (22 mg, 33%).

NMR (CD<sub>3</sub>OD, selected data for the hydrochloride salt) : 1.5 (s, 3H), 1.8 (m, 2H), 2.8 - 3.15 (m, 11H), 7.0 - 7.3 (m, 7H), 7.4 (d, 1H), 7.8 (d, 1H), 8.0 (br, 1H).

15 MS (thermospray) : M/Z (MH<sup>+</sup>) 410.2; C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 410.2.

#### Example 98

*N*-(3-{6-Methyl-3-[4-(trifluoromethyl)phenethyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



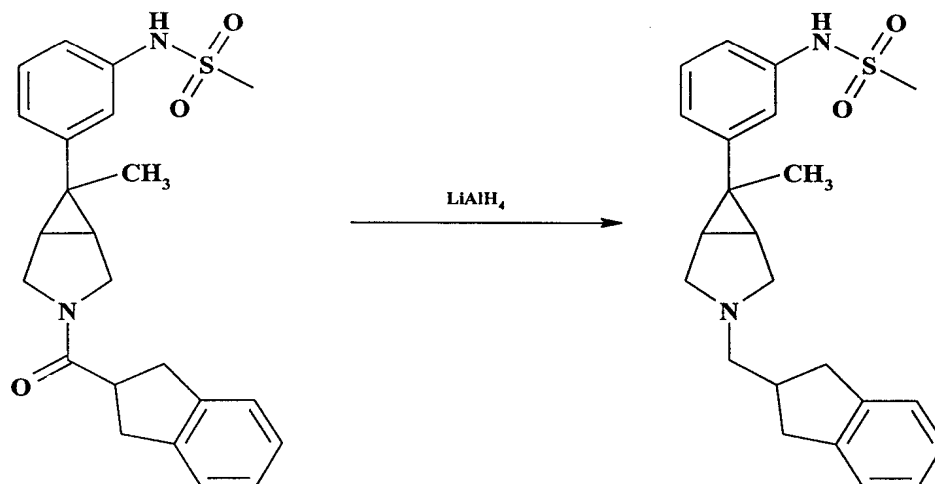
A solution of *N*-[3-(6-methyl-3-{2-[4-(trifluoromethyl)phenyl]acetyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 114, 65 mg, 0.144 mmol) in anhydrous tetrahydrofuran (1.0 ml) was stirred under a nitrogen atmosphere and cooled to 0 °C. The solution was treated dropwise with lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.28 ml, 0.28 mmol) and then stirred at room temperature for 18 h. The rapidly stirred reaction mixture was treated with water (0.28 ml), sodium hydrogen carbonate (200 mg) and ethyl acetate (15 ml) . After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. The residue was partially purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford an off-white solid. This was further purified by preparative HPLC (condition 8) to give the title compound as an off-white solid (22 mg, 35%, m.p. 159-161 °C).

NMR (CD<sub>3</sub>OD, selected data for the free base): 1.40 (s, 3H), 1.80 (m, 2H), 2.75-2.85 (m, 4H), 2.90 (s, 3H), 2.90-3.00 (m, 4H), 7.02 (m, 2H), 7.10 (br. s, 1H), 7.20 (dd, 1H), 7.40 (d, 2H), 7.75 (d, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 439.3; C<sub>22</sub>H<sub>25</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 439.2.

#### Example 99

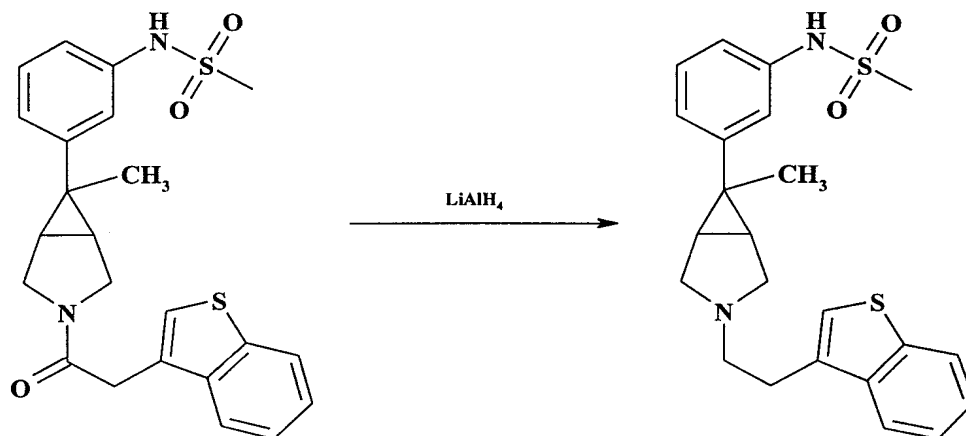
*N*-{3-[3-(2,3-Dihydro-1*H*-inden-2-yl)methyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



- To a solution of *N*-{3-[3-(2,3-dihydro-1*H*-inden-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Preparation 115, 94 mg, 0.23 mmol) in anhydrous tetrahydrofuran (2 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.40 ml, 0.40 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.40 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (15 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. This was purified by preparative HPLC (condition 8) to give a light brown oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml) and saturated brine (2 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (62 mg, 68%). The free base (55 mg, 0.14 mmol) was dissolved in anhydrous diethyl ether (5 ml) and dichloromethane (1 ml) and the solution was treated with hydrogen chloride (1.0M solution in diethyl ether, 0.153 ml). The heterogeneous suspension was concentrated *in vacuo* to afford the hydrochloride salt of the title compound as a white solid (50 mg, 83%).
- NMR (CD<sub>3</sub>OD, selected data for the hydrochloride salt) : 1.50 (s, 3H), 2.40 (m, 2H), 2.70-2.90 (m, 3H), 2.95 (s, 3H), 3.05-3.30 (m, 4H), 3.40-3.60 (m, 3H), 4.18 (br. d, 1H), 7.00-7.37 (m, 8H).
- MS (thermospray) : M/Z (MH<sup>+</sup>) 397.5; C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 397.2.

Example 100

N-(3-{3-[2-(1-Benzothiophene-3-yl)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of *N*-(3-{3-[2-(1-benzothiophen-3-yl)]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 116, 87 mg, 0.2 mmol) in anhydrous tetrahydrofuran (2 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.40 ml, 0.40 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.40 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (15 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. This was purified by preparative HPLC (condition 8) to give a light brown oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (45 mg, 53%).

NMR (CDCl<sub>3</sub>, selected data) : 1.50 (s, 3H), 1.85 (br., 2H), 2.90-3.20 (m, 11H), 7.00-7.15 (m, 3H), 7.15-7.30 (m, 2H), 7.30-7.45 (m, 2H), 7.80 (d, 1H), 7.85 (d, 1H).

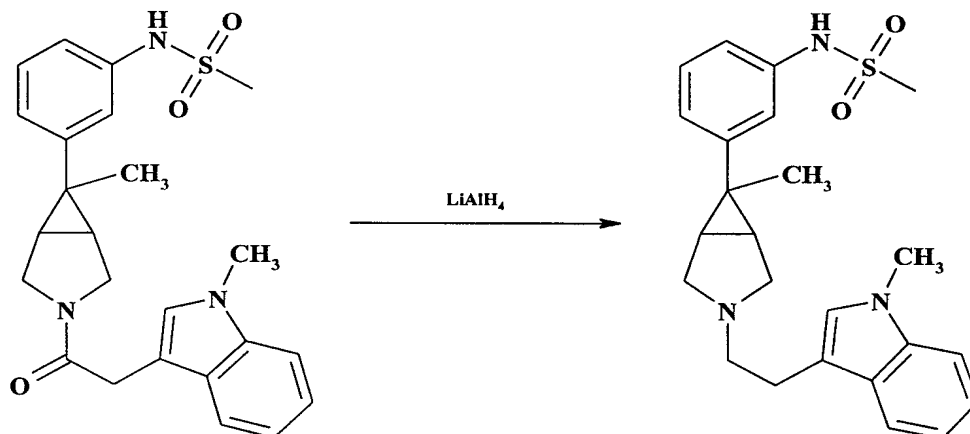
MS (thermospray) : M/Z (MH<sup>+</sup>) 427.3; C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 427.2.

Example 101

N-(3-{6-Methyl-3-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methane sulphonamide

25





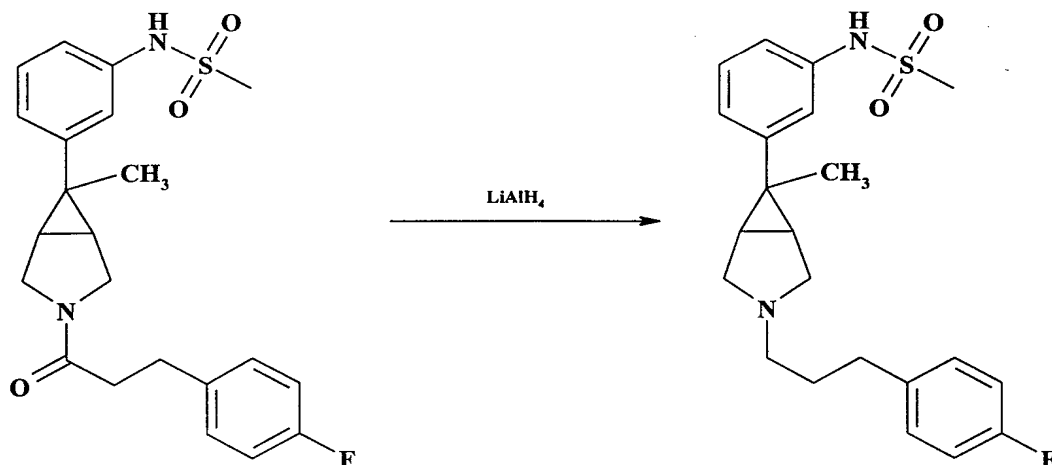
To a solution of *N*-(3-{6-methyl-3-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 117, 55 mg, 0.126 mmol) in anhydrous tetrahydrofuran (1 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.26 ml, 0.26 mmol) and the reaction mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.26 ml), sodium hydrogen carbonate (250 mg) and ethyl acetate (10 ml). After 30 min, the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. This was purified by preparative HPLC (condition 8) to give a pale yellow oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (28 mg, 52%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.50 (br. s, 3H), 1.85 (m, 2H), 2.80-3.20 (m, 11H), 3.75 (s, 3H), 6.90 (s, 1H), 7.00-7.18 (m, 4H), 7.20-7.35 (m, 3H), 7.66 (d, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 424.1; C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 424.2.

## 20 Example 102

*N*-(3-{3-[3-(4-Fluorophenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

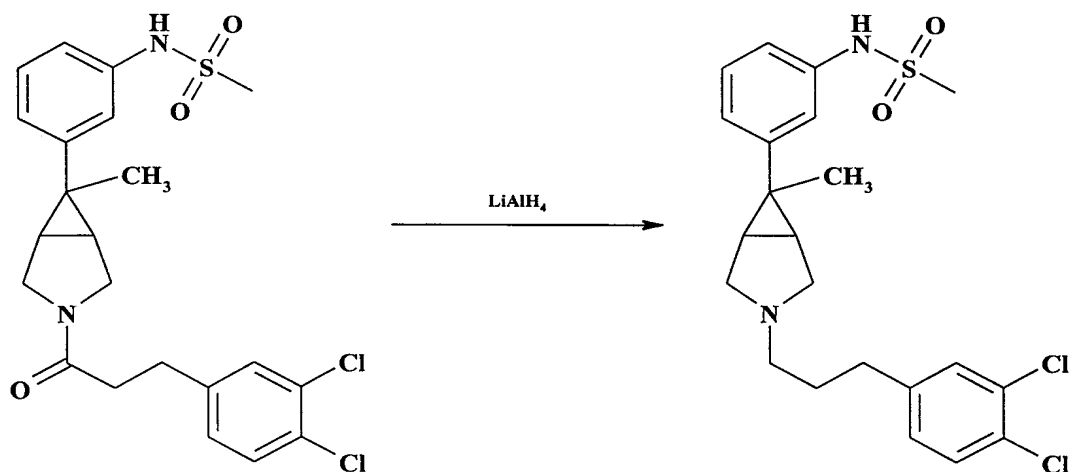


To a solution of *N*-(3-{3-[3-(4-fluorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 118, 86 mg, 0.21 mmol) in anhydrous tetrahydrofuran (2 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.42 ml, 0.42 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.42 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (10 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. The oil was purified by preparative HPLC (condition 8) to give a pale yellow oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (52 mg, 62%). The free base (45 mg, 0.112 mmol) was dissolved in anhydrous diethyl ether (5 ml) and dichloromethane (1 ml) and the solution was treated with hydrogen chloride (1.0M solution in diethyl ether, 0.123 ml). The heterogeneous suspension was concentrated *in vacuo* to afford the hydrochloride salt of the title compound as a white solid (46 mg, 94%).

NMR ( $\text{CD}_3\text{OD}$ , selected data for the hydrochloride) : 1.45 (s, 3H), 2.00 (m, 2H), 2.35 (m, 2H), 2.70 (m, 2H), 2.95 (s, 3H), 3.00-3.40 (m, 6H), 7.00-7.15 (m, 4H), 7.20-7.35 (m, 4H). MS (thermospray) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 403.3;  $\text{C}_{22}\text{H}_{27}\text{FN}_2\text{O}_2\text{S} + \text{H}$  requires 403.2.

### Example 103

*N*-(3-{3-[3-(3,4-Dichlorophenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

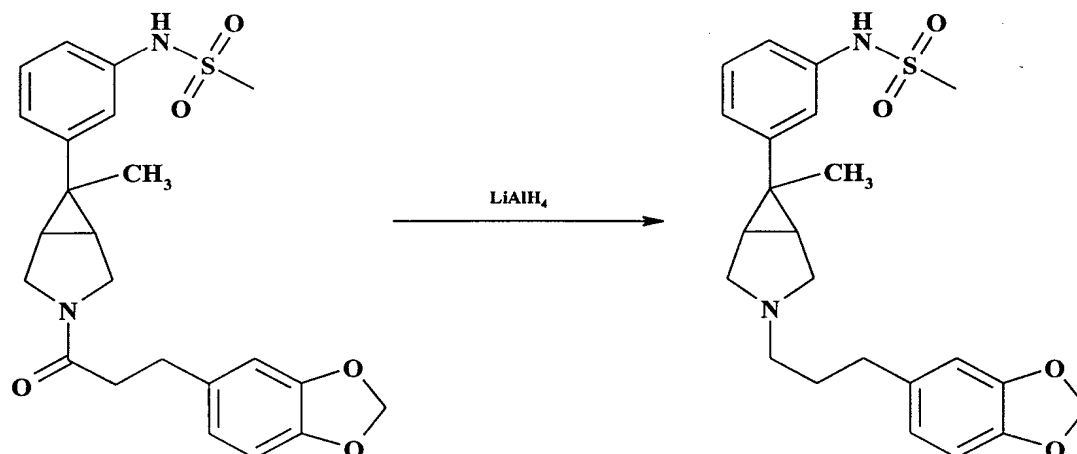
To a solution of *N*-(3-{3-[3-(3,4-dichlorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 119, 30 mg, 0.06 mmol) in anhydrous tetrahydrofuran (1 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.12 ml, 0.12 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.12 ml), sodium hydrogen carbonate (200 mg) and ethyl acetate (10 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to give a colourless oil. This was purified by preparative HPLC (condition 8) to afford the title compound as a pale yellow oil (5.2 mg, 19%).

15 MS (thermospray) : M/Z (MH<sup>+</sup>) 453.1; C<sub>22</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 453.1.

Example 104

*N*-(3-{3-[3-(1,3-Benzodioxol-5-yl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

20



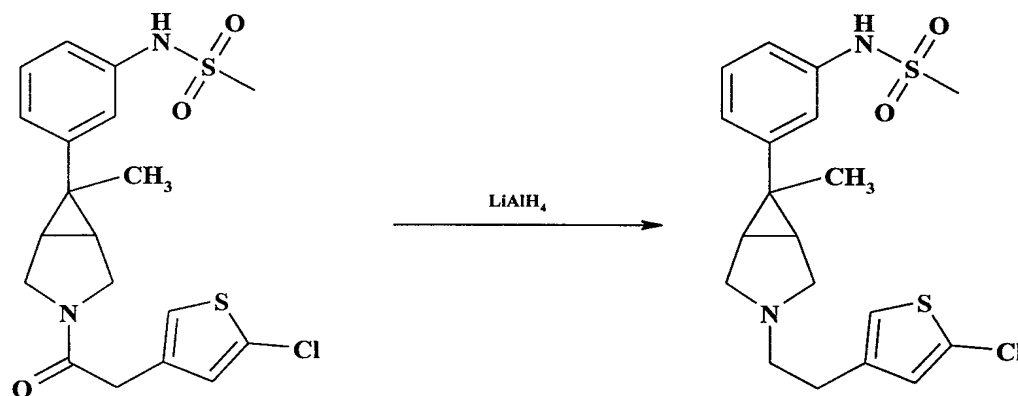
To a solution of *N*-(3-{3-[3-(1,3-benzodioxol-5-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 120, 96 mg, 0.22 mmol) in anhydrous tetrahydrofuran (2 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.44 ml, 0.44 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.44 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (10 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil. This was purified by preparative HPLC (condition 8) to give a pale yellow oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (32 mg, 34%). The free base (23 mg, 0.054 mmol) was dissolved in anhydrous diethyl ether (5 ml) and dichloromethane (1 ml) and the solution was treated with hydrogen chloride (1.0M solution in diethyl ether, 0.06 ml). The heterogeneous suspension was concentrated *in vacuo* to afford the hydrochloride salt of the title compound as a white solid (20 mg, 80%).

NMR (CD<sub>3</sub>OD, selected data for the hydrochloride salt) : 1.45 (s, 3H), 1.95 (br., 2H), 2.35 (m, 2H), 2.65 (m, 2H), 2.95 (s, 3H), 3.00-3.40 (m, 6H), 5.90 (m, 2H), 6.65-6.80 (m, 3H), 7.05-7.35 (m, 4H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 429.0; C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S + H requires 429.2.

#### Example 105

N-(3-{3-[2-(5-Chloro-3-thienyl)ethyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of *N*-(3-{3-[2-(5-chloro-3-thienyl)acetyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 121, 45 mg, 0.11 mmol) in anhydrous tetrahydrofuran (1 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.22 ml, 0.22 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.22 ml), sodium hydrogen carbonate (200 mg) and ethyl acetate (10 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a pale yellow oil. This was purified by preparative HPLC (condition 8) to give a very pale yellow oil which was partitioned between dichloromethane (10 ml) and aqueous potassium carbonate solution (4% w:v, 5 ml). The layers were separated and the organic layer was washed with water (3 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (14 mg, 33%).

10

15

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.25 (s, 3H), 1.80 (m, 2H), 2.75-3.10 (m, 11H), 6.60 (m, 1H), 6.70 (m, 1H), 7.00-7.15 (m, 3H), 7.25 (m, 1H).

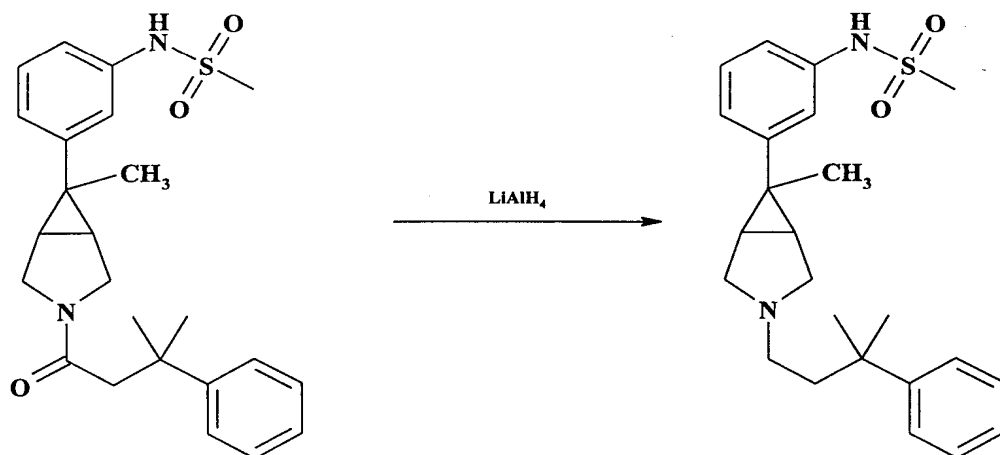
20

MS (electrospray) : M/Z (MH<sup>+</sup>) 411.1; C<sub>19</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 411.1.

Example 106

N-{3-[6-Methyl-3-(3-methyl-3-phenylbutyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl}methanesulfonamide

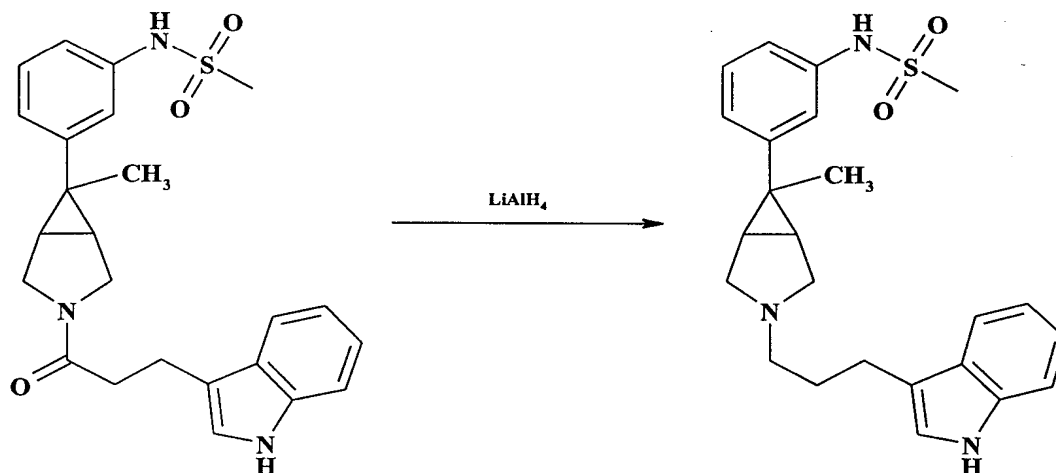
25



- To a solution of *N*-{3-[6-methyl-3-(3-methyl-3-phenylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Preparation 122, 59 mg, 0.138 mmol) in anhydrous tetrahydrofuran (1 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.28 ml, 0.28 mmol) and the mixture was stirred at room temperature for 3 h. The rapidly stirred reaction mixture was treated sequentially with water (0.28 ml), sodium hydrogen carbonate (200 mg) and ethyl acetate (10 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a pale yellow oil. This was purified by preparative HPLC (condition 8) to give a light brown oil which was partitioned between dichloromethane (15 ml) and aqueous potassium carbonate solution (7% w:v, 5 ml). The layers were separated and the organic layer was washed with water (5 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (38 mg, 66%).
- NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.30 (s, 6H), 1.40 (s, 3H), 1.70-1.90 (m, 4H), 2.35 (m, 2H), 2.80-3.00 (m, 4H), 3.00 (s, 3H), 7.00-7.10 (m, 3H), 7.15-7.40 (m, 6H). MS (thermospray) : M/Z (MH<sup>+</sup>) 413.2; C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 413.2.

#### Example 107

- N*-(3-{3-[3-(1*H*-Indol-3-yl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



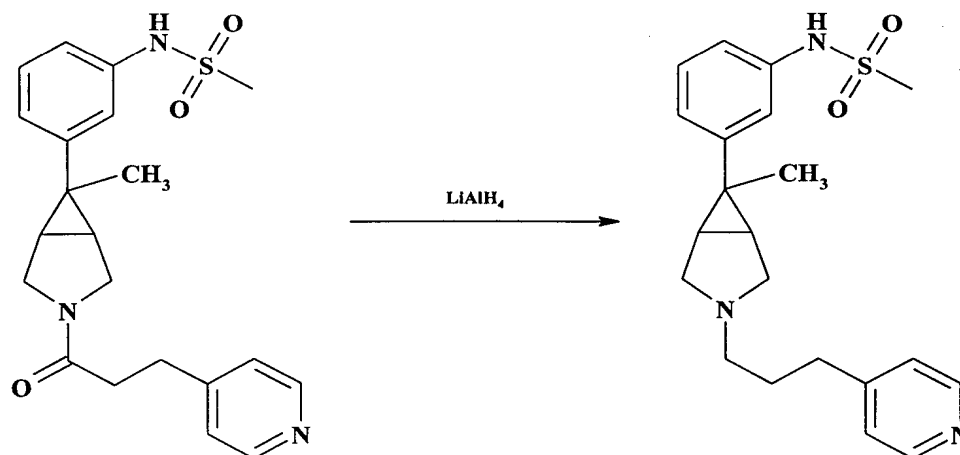
To a solution of *N*-(3-{3-[3-(1*H*-indol-3-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 123, 135 mg, 0.34 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.68 ml, 0.68 mmol) and the mixture was stirred at room temperature for 20 h. The rapidly stirred reaction mixture was treated sequentially with water (0.68 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (15 ml). After 30 min the reaction mixture was filtered and concentrated *in vacuo* to afford a glassy oil. This was purified by preparative HPLC (condition 8) to give a light brown oil which was partitioned between dichloromethane (15 ml) and aqueous potassium carbonate solution (7% w:v, 5 ml). The layers were separated and the organic layer was washed with water (5 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (69 mg, 50%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.57 (s, 3H), 1.80 (m, 2H), 1.80-2.00 (m, 2H), 2.60 (m, 2H), 2.75-3.10 (m, 9H), 7.00-7.30 (m, 7H), 7.35 (d, 1H), 7.60 (d, 1H), 7.95 (br., 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 424.2; C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 424.2.

#### 20 Example 108

*N*-(3-{6-Methyl-3-[3-(4-pyridinyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of *N*-(3-{6-methyl-3-[3-(4-pyridinyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 124, 100 mg, 0.25 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) and the mixture was stirred at 10 °C for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (0.40 ml), sodium hydrogen carbonate (400 mg) and ethyl acetate (20 ml). After 18 h the reaction mixture was filtered and concentrated *in vacuo* to afford a colourless oil (70 mg). The free base was dissolved in anhydrous diethyl ether (5 ml) and dichloromethane (1 ml) and the solution was treated with hydrogen chloride (1.0M solution in diethyl ether, 0.18 ml). Excess diethyl ether was decanted from the resulting precipitate and the remaining suspension was concentrated *in vacuo* to afford the hydrochloride salt of the title compound as a white solid (64 mg, 83%).

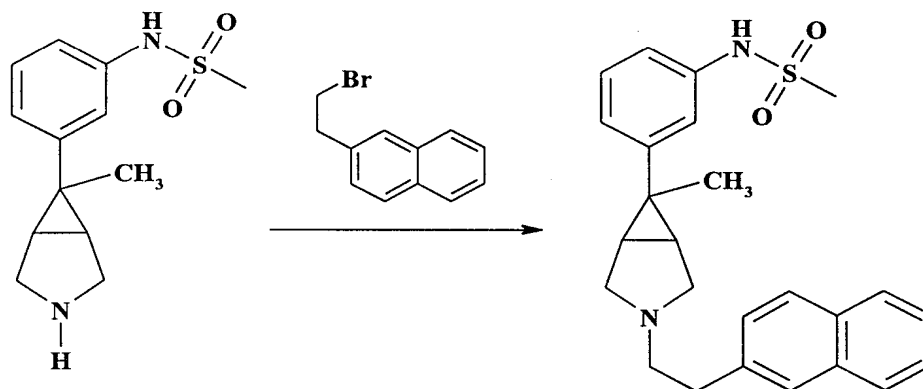
NMR (CD<sub>3</sub>OD, selected data for the hydrochloride salt) : 1.45 (br., 3H), 2.10 (m, 2H), 2.38 (m, 2H), 2.82 (m, 2H), 2.95 (m, 3H), 3.08 (m, 1H), 3.22-3.40 (m, 4H), 4.05 (m, 1H), 7.05-7.15 (m, 2H), 7.20 (s, 1H), 7.28 (dd, 1H), 7.50 (d, 2H), 8.55 (d, 2H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 386.2; C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 386.2.

#### Example 109

*N*-(3-{6-Methyl-3-[2-(2-naphthyl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide





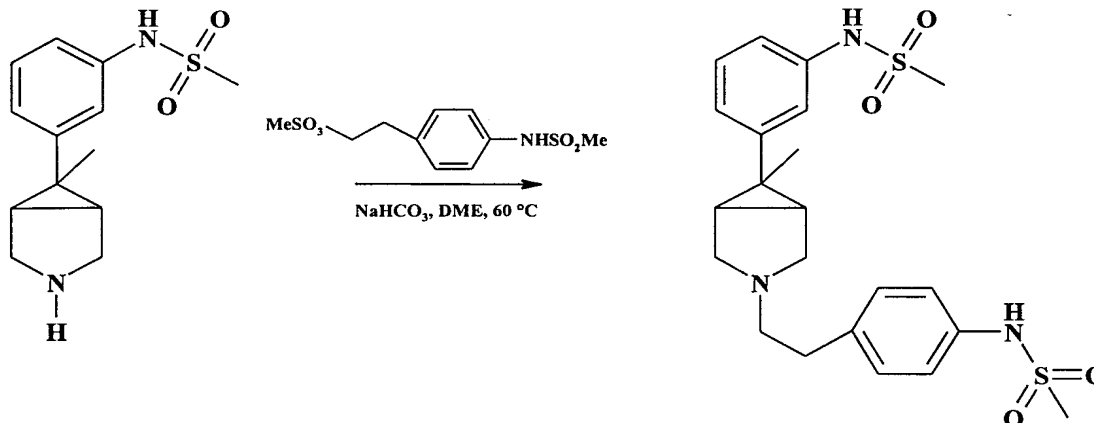
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 122 mg, 0.404 mmol) in *N,N*-dimethylformamide (4 ml) was added 2-(2-bromoethyl)naphthalene (A. K. Mitra, R. C. Bannerjee and R. Bhattacharya, J. Ind. Chem. Soc., 1971, 48, 391, 95 mg, 0.404 mmol) and sodium hydrogen carbonate (102 mg 1.212 mmol). The reaction mixture was heated at 80°C for 6 h before allowing to cool to room temperature. The mixture was partitioned between water (5 ml) and dichloromethane (5 ml), and the aqueous layer was extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a brown oil (130 mg). The residue was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.88 ammonia (400 : 8 : 1) to afford the title compound as a pale yellow oil. The free base was dissolved in anhydrous diethyl ether (2 ml) and dichloromethane (0.5 ml) and the solution was treated with hydrogen chloride (1.0M solution in diethyl ether, 0.15 ml). The resulting suspension was concentrated *in vacuo* to afford the hydrochloride salt of the title compound as a pale yellow solid (52 mg, 28%).

NMR (CD<sub>3</sub>OD, for the hydrochloride salt) : 1.28 (m, 2H), 1.50 (br., 3H), 2.38 (m, 2H), 2.95 (s, 3H), 3.10-3.25 (m, 3H), 3.55-3.65 (m, 3H), 4.10 (br., 1H), 7.05-7.15 (m, 2H), 7.22-7.35 (m, 2H), 7.45-7.55 (m, 3H), 7.80-7.92 (m, 4H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 421.2; C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 421.2.

#### Example 110

*N*-[3-(6-methyl-3-{4-[(methylsulfonyl)amino]phenethyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



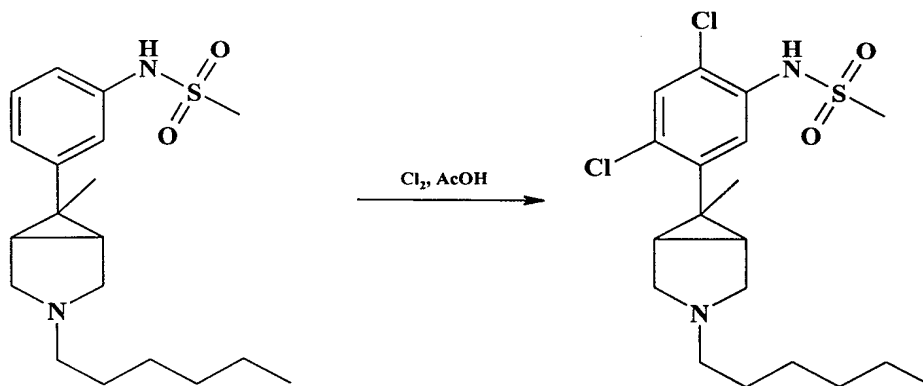
To a solution of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide hydrochloride salt (Preparation 53, 100 mg, 0.33 mmol) in ethylene glycol dimethyl ether (10 ml) was added sodium hydrogen carbonate (1.5 g, 18 mmol) and 4-[(methylsulfonyl)amino]phenethyl methanesulfonate (P. E. Cross, J. E. Arrowsmith, G. N. Thomas, R. P. Dickinson, DD 281 599 A5, 97 mg, 0.33 mmol) and the reaction mixture was heated at  $60^\circ\text{C}$  for 20 h. After cooling, diethyl ether (15 ml) and water (15 ml) were added and the reaction mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was further extracted with diethyl ether (2 x 10 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia solution (200 : 8 : 1) to afford the title compound as an oil. The oil was further purified by preparative HPLC (condition 9) to give the title compound as a colourless glass (11mg, 7%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 0.8-1.0(m, 2H), 1.2 (s, 3H), 1.5 (s, 6H), 1.9 (m, 1H), 2.8 (m, 2H), 3.0 (d, 6H), 3.1 (m, 2H), 7.0-7.3 (m, 8H)

MS (thermospray) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 464.0,  $\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_2 + \text{H}$  requires 464.1.

#### Example 111

*N*-[2,4-Dichloro-5-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



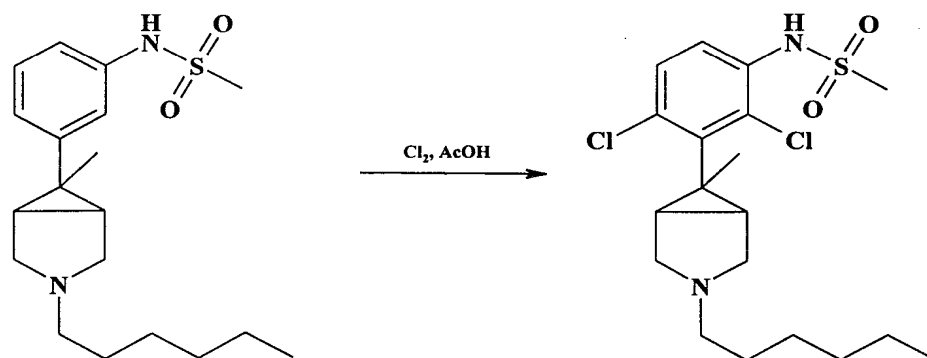
To a solution of *N*-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Example 6, 132 mg, 0.39 mmol) in dichloromethane (12 ml) at 0 °C was added dropwise chlorine (0.132 M solution in acetic acid, 2.94 ml, 0.39 mmol) over 30 min. The mixture was stirred for 3 h, slowly warming to room temperature. The reaction mixture was basified to pH 8 by careful addition of saturated aqueous potassium carbonate solution and the resulting mixture was stirred at room temperature for 15 hours. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residual oil was purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (100 : 2 : 1 then 100: 4: 1) to give a mixture of two products. The two products were separated by preparative HPLC (condition 10) to afford firstly the title compound as a colourless glass (12 mg, 7%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 0.90 (m, 3H), 1.20-1.40 (m, 7H), 1.40-1.50 (m, 4H), 1.75 (m, 2H), 2.40 (m, 2H), 2.80 (m, 2H), 3.00-3.10 (m, 5H), 7.40 (s, 1H), 7.60 (s, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 419.0; C<sub>19</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 419.1.

#### Example 112

*N*-[2,4-Dichloro-3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



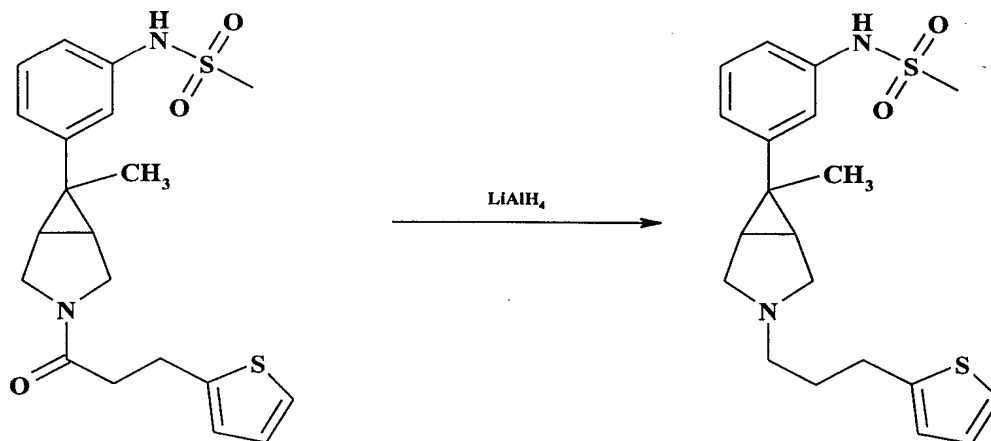
To a solution of *N*-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Example 6, 132 mg, 0.39 mmol) in dichloromethane (12 ml) at 0°C was added dropwise chlorine (0.132 M solution in acetic acid, 2.94 ml, 0.39 mmol) over 30 min. The mixture was stirred for 3 h, slowly warming to room temperature. The reaction mixture was basified to pH 8 by careful addition of saturated aqueous potassium carbonate solution and the resulting mixture was stirred at room temperature for 15 hours. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The residual oil was purified by chromatography using a Sep-Pak™ cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (100 : 2 : 1 then 100: 4: 1) to give a mixture of two products. The two products were separated by preparative HPLC (condition 10) to afford firstly *N*-[2,4-Dichloro-5-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide as a colourless glass (Example 111, 12 mg, 7%). Further elution using preparative HPLC (condition 10) afforded the title compound as a colourless glass (11 mg, 7%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 0.90 (m, 3H), 1.20-1.40 (m, 7H), 1.40-1.50 (m, 4H), 1.75 (m, 1H), 1.85 (m, 1H), 2.45 (m, 2H), 2.80 (m, 2H), 3.00 (m, 3H), 3.10 (m, 2H), 7.25 (d, 1H), 7.45 (d, 1H).

MS (electrospray) :  $M/Z$  ( $\text{MH}^+$ ) 419.0;  $\text{C}_{19}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_2\text{S} + \text{H}$  requires 419.1.

### Example 113

*N*-(3-{6-Methyl-3-[3-(2-thienyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



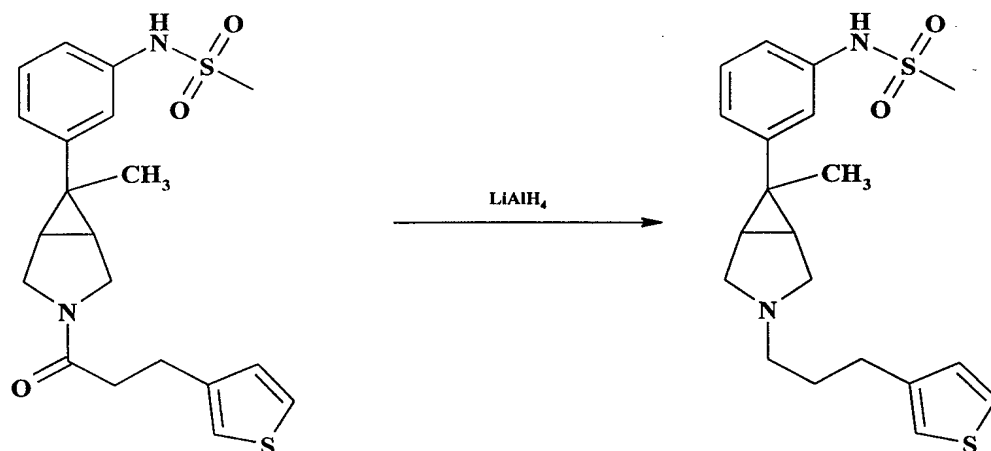
To a solution of *N*-(3-{6-methyl-3-[3-(2-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 125, 200 mg, 0.49 mmol) in anhydrous tetrahydrofuran (7.5 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.99 ml, 0.99 mmol) and the mixture was stirred at room temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (1.0 ml), sodium hydrogen carbonate (1.0 g) and ethyl acetate (25 ml). After 15 min the reaction mixture was filtered and concentrated *in vacuo* to afford a light yellow oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100) to afford the title compound as a colourless oil (135 mg, 70%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.55 (s, 3H), 1.75-1.90 (m, 4H), 2.50-2.70 (m, 2H), 2.85-3.10 (m, 9H), 6.80 (m, 1H), 6.95 (m, 1H), 7.00-7.15 (m, 4H), 7.20-7.30 (m, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 391.1; C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 391.1.

#### Example 114

*N*-(3-{6-Methyl-3-[3-(3-thienyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



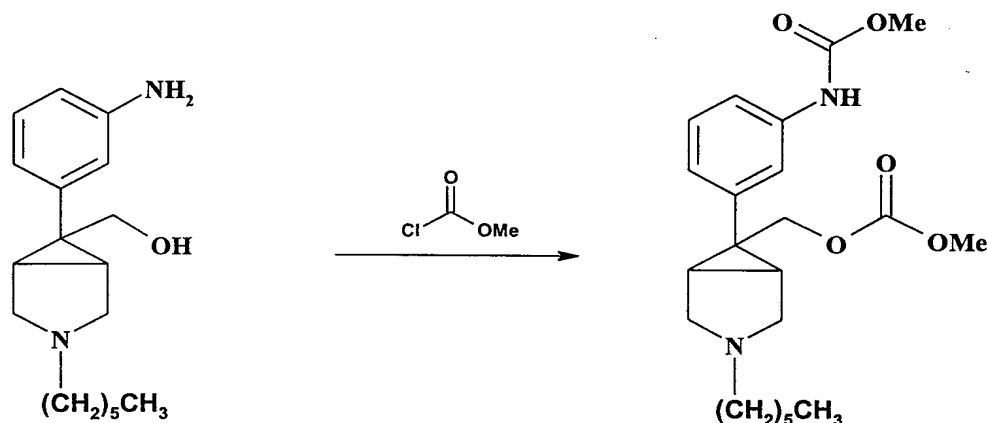
To a solution of *N*-(3-{6-methyl-3-[3-(3-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 126, 200 mg, 0.49 mmol) in anhydrous  
 5 tetrahydrofuran (7.5 ml) under a nitrogen atmosphere at 0°C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.99 ml, 0.99 mmol) and the mixture was stirred at room temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (1 ml), sodium hydrogen carbonate (1.0 g) and ethyl acetate (25 ml). After 15 min the reaction mixture was filtered and concentrated *in vacuo* to afford a  
 10 light yellow oil. This was purified by chromatography using a Biotage Flash 12 <sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100) to afford the title compound as a colourless oil (108 mg, 56%).

NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.55 (s, 3H), 1.70-1.90 (m, 4H), 2.45-2.60 (m, 2H), 2.70 (m, 2H), 2.80-3.10 (m, 7H), 6.95 (d, 2H), 7.00-7.15 (m, 3H), 7.20-7.30 (m,  
 15 2H).

MS (electrospray) :  $M/Z$  ( $\text{MH}^+$ ) 391.1;  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\text{S}_2 + \text{H}$  requires 391.1.

#### Example 115

(3-Hexyl-6-{3-[(methoxycarbonyl)amino]phenyl}-3-azabicyclo[3.1.0]hex-6-yl)methyl  
 20 methyl carbonate

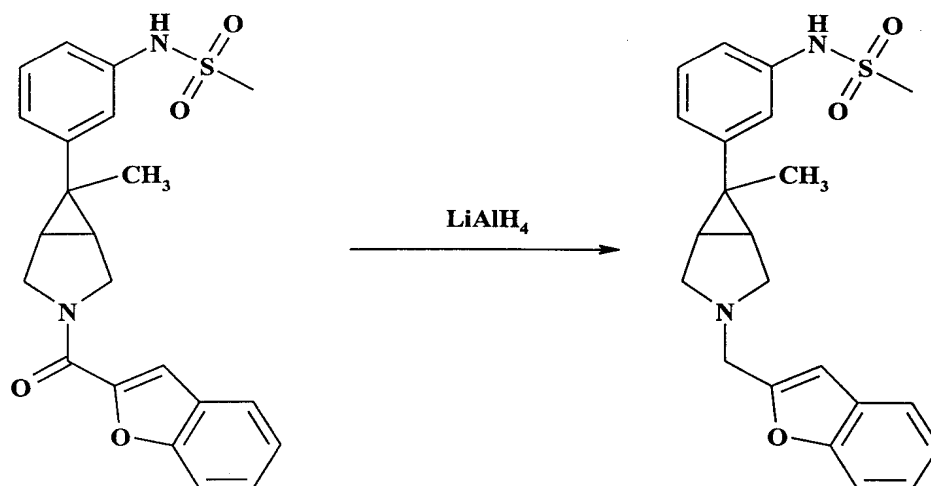


A solution of [6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methanol  
 5 (Preparation 94, 0.03 g, 0.09 mmol) in tetrahydrofuran (1 ml) was stirred at 0°C under an  
 atmosphere of nitrogen. The reaction mixture was treated with triethylamine (0.03 ml,  
 0.19 mmol) followed by dropwise addition of methyl chloroformate (0.01 ml, 0.17 mmol).  
 The reaction mixture was allowed to warm to room temperature and stirred for 2 h before  
 pouring onto aqueous saturated sodium hydrogen carbonate (50 ml). The product was  
 10 extracted with ethyl acetate (3 x 25 ml) and the combined organic extracts were dried  
 (Na<sub>2</sub>SO<sub>4</sub>) and then concentrated *in vacuo* to give a brown residue. The crude product was  
 purified by preparative HPLC (condition 11) to give a clear glass (6 mg, 15% yield).  
 NMR (CD<sub>3</sub>OD, selected data for the free base) : 1.55 (m, 2H), 2.10 (m, 1H), 3.55 (m, 2H),  
 3.70 (s, 3H), 3.75 (s, 3H), 4.0-4.15 (m, 3H), 4.25 (m, 1H), 6.85 (d, 1H), 7.19-7.35 (m, 3H).

15

### Example 116

N-{3-[3-(1-Benzofuran-2-yl)methyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



To a suspension of *N*-{3-[3-(1-benzofuran-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Preparation 127, 200 mg, 0.487 mmol) in anhydrous tetrahydrofuran (5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.97 ml, 0.97 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (1.0 ml), sodium hydrogen carbonate (1.0 g) and ethyl acetate (15 ml). After 5 min, the reaction mixture was filtered and concentrated *in vacuo* to afford 180 mg of a pale yellow oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100 over 30 min) then ethyl acetate : methanol (100 : 0 to 0 : 100 over 15 min) to afford the title compound as a white foam (136 mg, 70%).

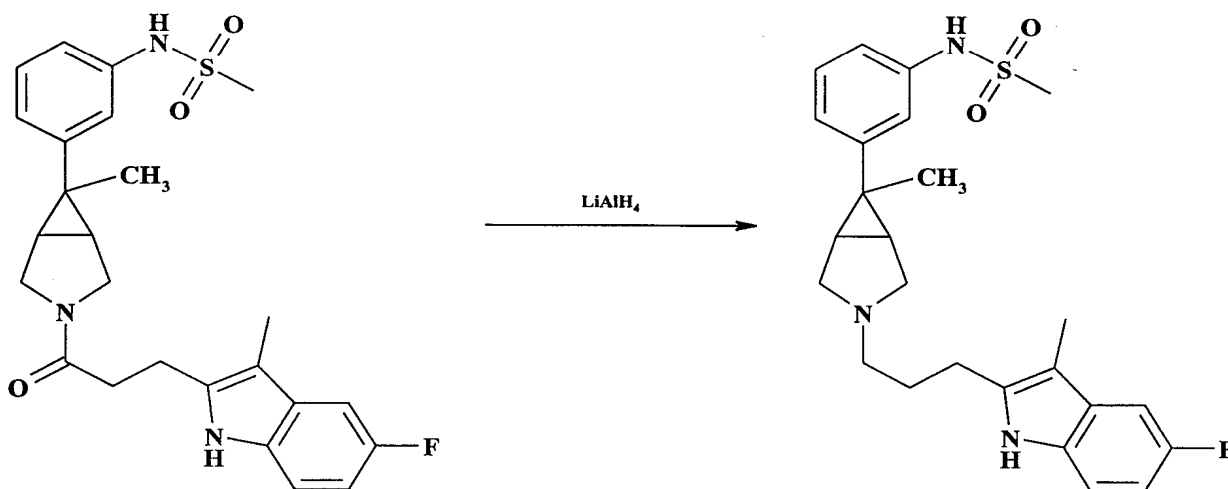
NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.55 (s, 3H), 1.83 (m, 2H), 3.00 (s, 3H), 3.05-3.20 (m, 4H), 3.88 (m, 2H), 6.40-6.70 (m, 2H), 7.00-7.13 (m, 3H), 7.18-7.35 (m, 2H), 7.45 (d, 1H), 7.55 (d, 1H).

MS (electrospray) : *M/Z* (MH<sup>+</sup>) 397.4; C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 397.2.

#### Example 117

*N*-(3-{3-[3-(5-Fluoro-3-methyl-1*H*-indol-2-yl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide





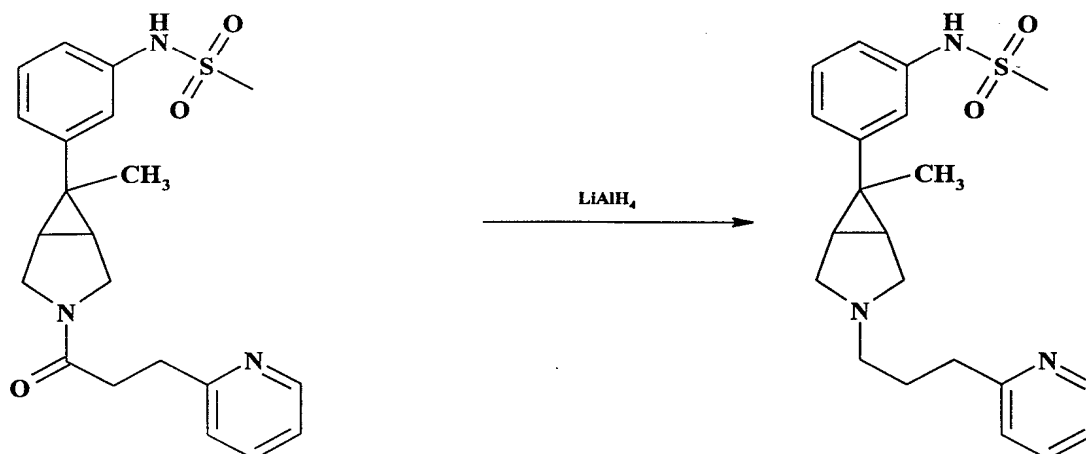
To a solution of *N*-(3-{3-[3-(5-fluoro-3-methyl-1*H*-indol-2-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 128, 100 mg, 0.213 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.42 ml, 0.42 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (0.45 ml), sodium hydrogen carbonate (450 mg) and ethyl acetate (10 ml). After 5 min, the reaction mixture was filtered and concentrated *in vacuo* to afford 95 mg of a colourless oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100 over 30 min) then ethyl acetate : methanol (100 : 0 to 0 : 100 over 15 min) to afford the title compound as a white foam (56 mg, 46%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.55 (s, 3H), 1.80-1.93 (m, 4H), 2.20 (s, 3H), 2.59 (t, 2H), 2.83 (t, 2H), 3.00-3.10 (m, 7H), 6.83 (ddd, 1H), 7.00-7.15 (m, 4H), 7.18 (dd, 1H), 7.24 (m, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 456.2; C<sub>25</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>2</sub>S + H requires 456.2.

## Example 118

*N*-(3-{6-Methyl-3-[3-(2-pyridinyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



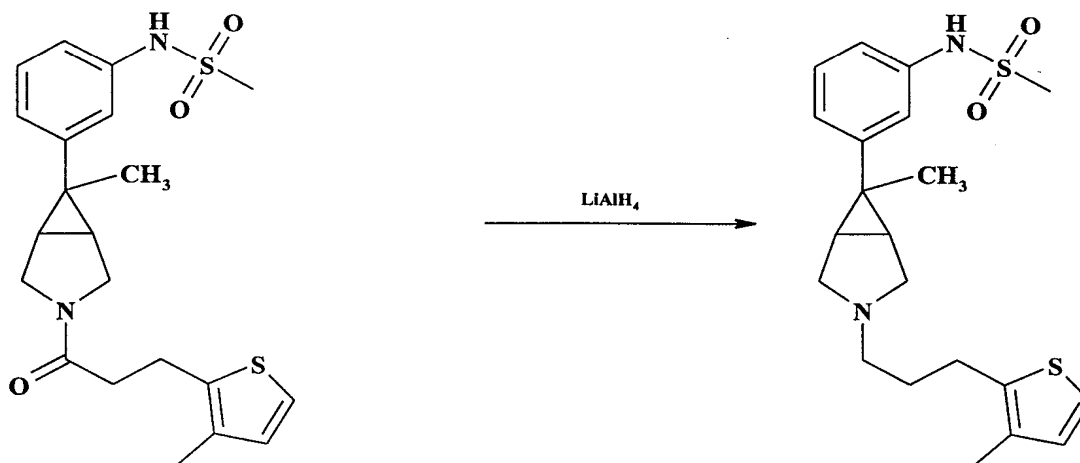
To a solution of *N*-(3-{6-methyl-3-[3-(2-pyridinyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 129, 16 mg, 0.04 mmol) in anhydrous tetrahydrofuran (2 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 80 µl, 80 µmol) and the reaction mixture was stirred at room temperature for 5 h. The rapidly stirred reaction mixture was treated sequentially with water (100 µl), sodium carbonate (100 mg) and ethyl acetate (5 ml). After 5 min, the reaction mixture was filtered and concentrated *in vacuo* to afford 10 mg of a colourless oil. This was purified by chromatography using silica gel (1 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to afford the title compound as a colourless oil (3 mg, 19%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.55 (s, 3H), 1.75 (m, 2H), 1.90 (t, 2H), 2.50 (t, 2H), 2.75-2.88 (m, 4H), 3.00 (s, 3H), 3.05 (d, 2H), 7.00 (d, 1H), 7.05-7.30 (m, 5H), 7.60 (d, 1H), 8.55 (d, 1H).

MS (electrospray) : *M/Z* (MH<sup>+</sup>) 386.2; C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 386.2.

#### Example 119

*N*-(3-{6-Methyl-3-[3-(3-methyl-2-thienyl)propyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



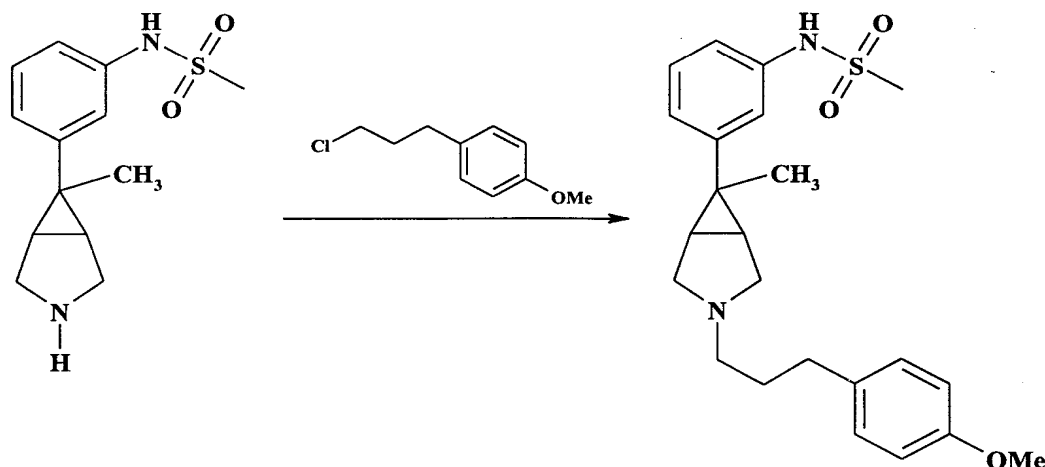
To a solution of *N*-(3-{6-methyl-3-[3-(3-methyl-2-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 130, 150 mg, 0.358 mmol) in anhydrous tetrahydrofuran (10 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.72 ml, 0.72 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (0.75 ml), sodium hydrogen carbonate (750 mg) and ethyl acetate (15 ml). After 15 min, the reaction mixture was filtered and concentrated *in vacuo* to afford 140 mg of a colourless oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100 over 30 min) and then with ethyl acetate : methanol (100 : 0 to 0 : 100 over 5 min) to afford the title compound as a colourless oil (74 mg, 50%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.57 (s, 3H), 1.75-1.90 (m, 4H), 2.18 (s, 3H), 2.58 (m, 2H), 2.79 (t, 2H), 2.82-3.12 (m, 7H), 6.78 (d, 1H), 7.00-7.15 (m, 4H), 7.25 (m, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 405; C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 405.

#### Example 120

*N*-(3-{3-[3-(4-methoxyphenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



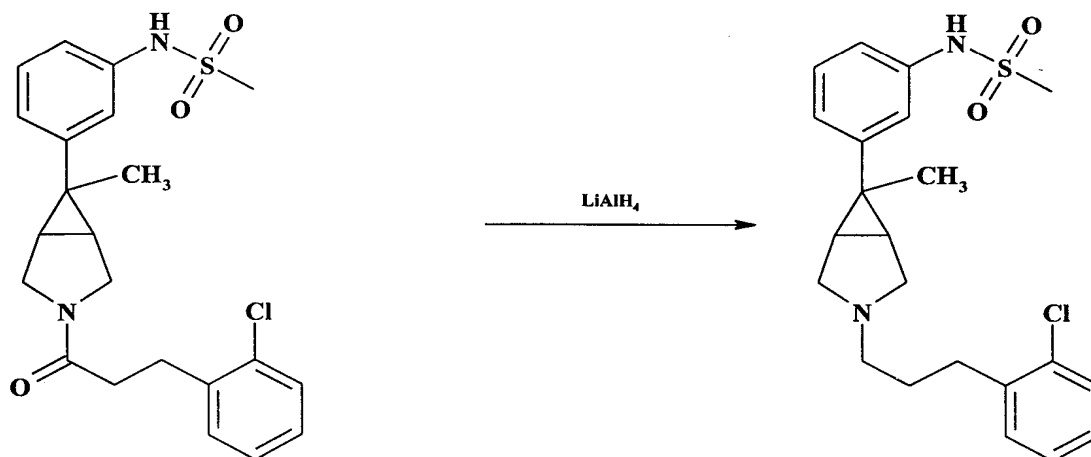
To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 450 mg, 1.50 mmol) in *N,N*-dimethylformamide (20 ml) was added sodium hydrogen carbonate (375 mg, 4.50 mmol), 1-(3-chloropropyl)-4-methoxybenzene (274 mg, 1.50 mmol) and sodium iodide (35 mg) and the reaction was heated at 55 °C for 3 d. The reaction mixture was concentrated *in vacuo* and the residue was treated with water (15 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with water (15 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford 570 mg of a brown gum. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.880 ammonia (250 : 8 : 1) to afford the title compound as a colourless oil (37 mg, 6%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.55 (s, 3H), 1.70-1.85 (m, 4H), 2.52 (t, 2H), 2.60 (t, 2H), 2.83-3.08 (m, 7H), 3.80 (s, 3H), 6.82 (d, 2H), 7.00-7.15 (m, 5H), 7.24 (dd, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 415; C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 415.

#### Example 121

*N*-(3-{3-[3-(2-Chlorophenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of *N*-(3-{3-[3-(2-chlorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 131, 100 mg, 0.231 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.25 ml, 0.25 mmol) and the reaction mixture was stirred at room temperature for 7 h. The rapidly stirred reaction mixture was treated sequentially with water (0.25 ml), sodium carbonate (250 mg) and ethyl acetate (2.5 ml). The reaction mixture was left to stir overnight and then was filtered and concentrated *in vacuo*. This was purified by chromatography using silica gel (2 g) eluting with ethyl acetate : hexane : 0.880 ammonia (60 : 40 : 1) to afford the title compound as a colourless oil (77 mg, 80%).

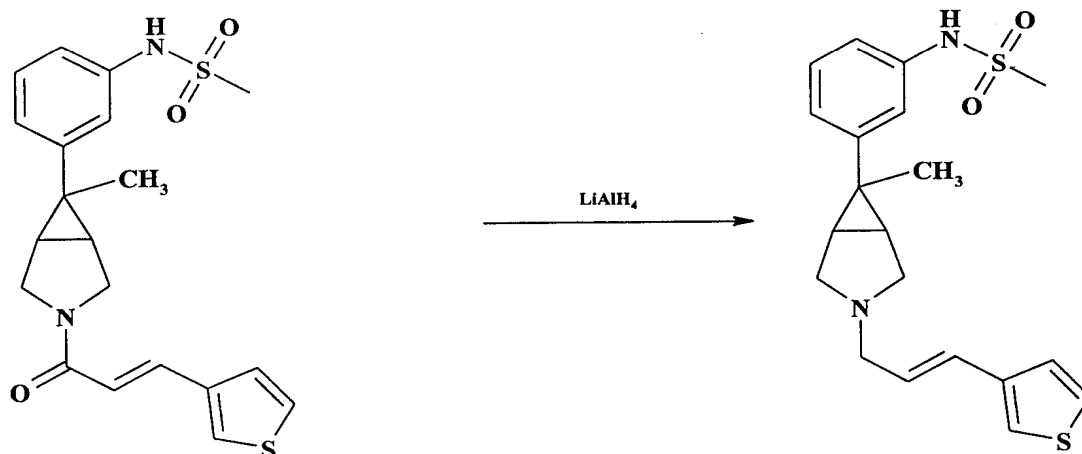
NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.70-1.80 (m, 4H), 2.52 (t, 2H), 2.65-2.82 (m, 4H), 3.00 (s, 3H), 3.03 (d, 2H), 7.00-7.38 (m, 8H).

MS (electrospray) : M/Z (M+H<sup>+</sup>) 419.2; C<sub>22</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>S + H requires 419.2.

IR  $\nu_{\max}$  (polyethylene card)/cm<sup>-1</sup> : 1607 (w), 1472 (w), 1325 (m), 1156 (s).

### Example 122

*N*-(3-{6-Methyl-3-[(*E*)-3-(3-thienyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of *N*-(3-{6-methyl-3-[(*E*)-3-(3-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 132, 100 mg, 0.248 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.25 ml, 0.25 mmol) and the reaction mixture was stirred at room temperature for 7 h. The rapidly stirred reaction mixture was treated sequentially with water (0.25 ml), sodium carbonate (250 mg) and ethyl acetate (2.5 ml). The reaction mixture was left to stir overnight and then was filtered and concentrated *in vacuo*. This was purified by chromatography using silica gel (2 g) eluting with ethyl acetate : hexane : 0.880 ammonia (60 : 40 : 1) to afford the title compound as a colourless oil (32 mg, 33%).

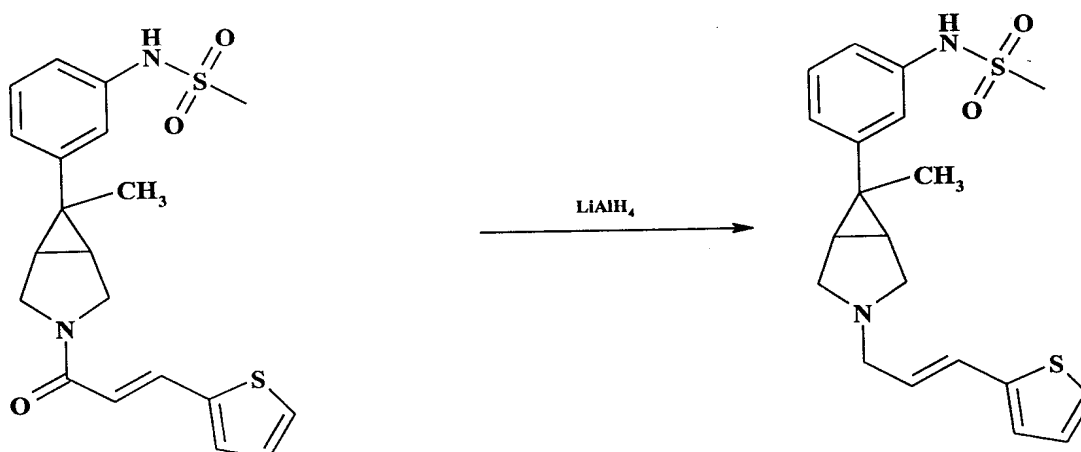
NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.78 (m, 2H), 2.42-2.95 (m, 2H), 3.00-3.10 (m, 5H), 3.25 (d, 2H), 6.05 (dt, 1H), 6.55 (d, 1H), 6.92-7.15 (m, 5H), 7.20-7.30 (m, 2H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 389.1; C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 389.1.

IR  $\nu_{\max}$  (polyethylene card)/cm<sup>-1</sup> : 1607 (w), 1472 (w), 1325 (m), 1155 (s), 971 (m).

### Example 123

*N*-(3-{6-Methyl-3-[(*E*)-3-(2-thienyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of  $N$ -(3-{6-methyl-3-[(*E*)-3-(2-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 133, 100 mg, 0.248 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.25 ml, 0.25 mmol) and the reaction mixture was stirred at room temperature for 7 h. The rapidly stirred reaction mixture was treated sequentially with water (0.25 ml), sodium carbonate (250 mg) and ethyl acetate (2.5 ml). The reaction mixture was left to stir overnight and then was filtered and concentrated *in vacuo*. This was purified by chromatography using silica gel (2 g) eluting with ethyl acetate : hexane : 0.880 ammonia (60 : 40 : 1) to afford the title compound as a pale yellow oil (67 mg, 69%).

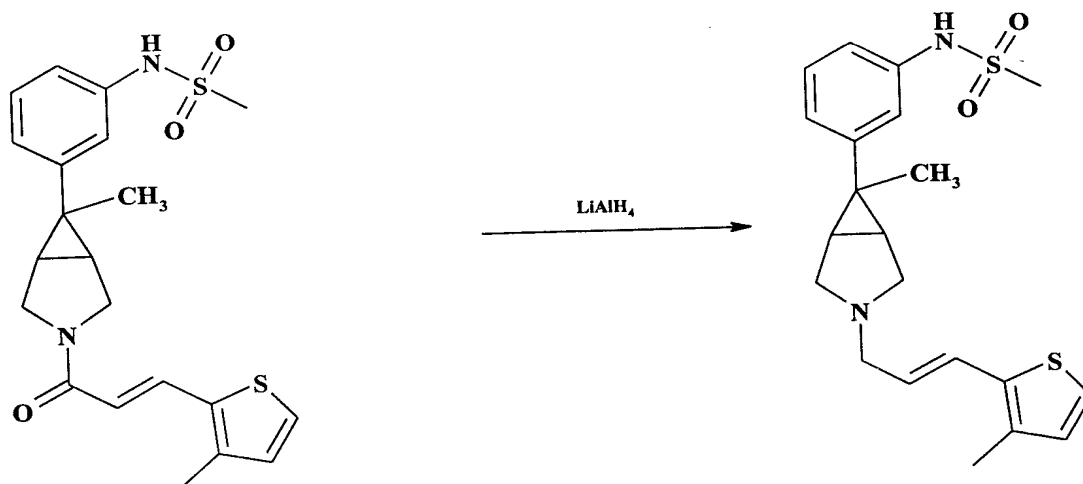
NMR ( $\text{CDCl}_3$ , selected data) : 1.58 (s, 3H), 1.80 (m, 2H), 2.95 (m, 2H), 3.00 (s, 3H), 3.04 (d, 2H), 3.23 (d, 2H), 6.10 (dt, 1H), 6.65 (d, 1H), 6.92-6.98 (m, 2H), 7.00-7.15 (m, 4H), 7.23 (m, 1H).

MS (electrospray) :  $M/Z$  ( $M+H^+$ ) 389.1;  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2 + \text{H}$  requires 389.1.

IR  $\nu_{\text{max}}$  (polyethylene card)/ $\text{cm}^{-1}$  : 1607 (w), 1472 (w), 1325 (m), 1155 (s), 974 (m).

#### Example 124

$N$ -(3-{6-Methyl-3-[(*E*)-3-(3-methyl-2-thienyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of *N*-(3-{6-methyl-3-[(*E*)-3-(3-methyl-2-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 134, 100 mg, 0.240 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.25 ml, 0.25 mmol) and the reaction mixture was stirred at room temperature for 7 h. The rapidly stirred reaction mixture was treated sequentially with water (0.25 ml), sodium carbonate (250 mg) and ethyl acetate (2.5 ml). The reaction mixture was left to stir overnight and then was filtered and concentrated *in vacuo*. This was purified by chromatography using silica gel (2 g) eluting with ethyl acetate : hexane : 0.880 ammonia (60 : 40 : 1) to afford the title compound as a very pale yellow oil (60 mg, 62%).

NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.78 (m, 2H), 2.02 (s, 3H), 2.90 (m, 2H), 3.00 (s, 3H), 3.05 (d, 2H), 3.27 (d, 2H), 6.00 (dt, 1H), 6.65 (d, 1H), 6.78 (d, 1H), 7.00-7.05 (m, 2H), 7.05-7.10 (m, 2H), 7.25 (m, 1H).

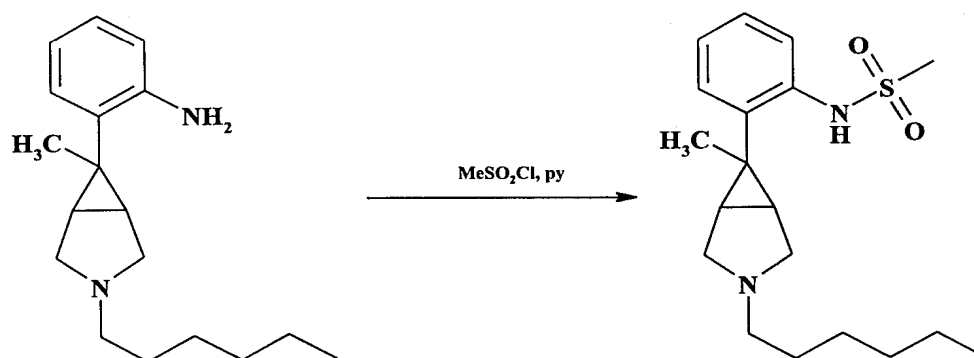
MS (electrospray) : M/Z (M+H<sup>+</sup>) 403.2; C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> + H requires 403.2.

IR ?<sub>max</sub> (polyethylene card)/cm<sup>-1</sup> : 2360 (m), 1607 (w), 1472 (w), 1325 (m), 1155 (s), 975 (m).

## 20 Example 125

*N*-(2-{3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



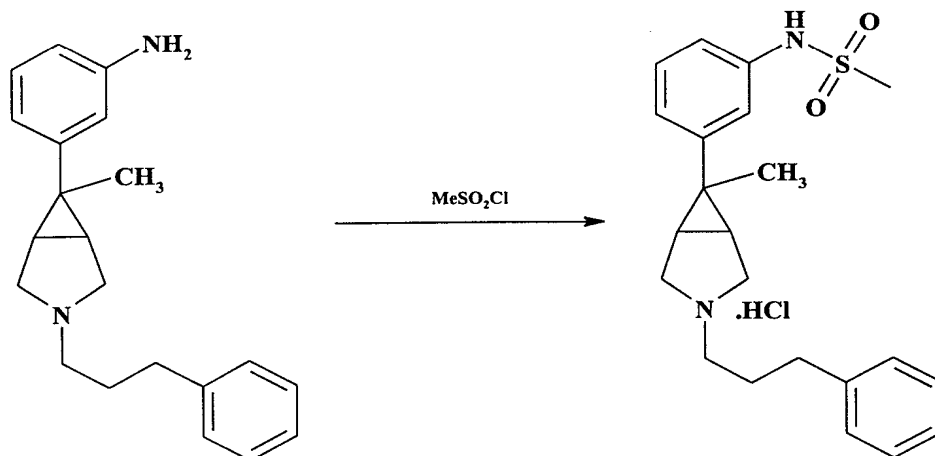


To a solution of 2-[3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 140, 30 mg, 0.11 mmol) in pyridine (1.0 ml) under a nitrogen atmosphere at room temperature was added dropwise methane sulfonyl chloride (13  $\mu\text{l}$ , 0.16 mmol), and the reaction mixture was stirred at room temperature for 2 d. Ice (2 g) and dichloromethane (5 ml) were added, the layers were separated and the aqueous layer was further extracted with dichloromethane (5 ml). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. This was purified by chromatography using silica gel (1.5 g) eluting with dichloromethane : ethanol : 0.880 ammonia (200 : 8 : 1) to afford the title compound as a very pale yellow oil (5.2 mg, 14%).

NMR ( $\text{CDCl}_3$ , selected data) : 0.88 (m, 3H), 1.20-1.40 (m, 6H), 2.18 (d, 1H), 2.40 (d, 1H), 3.15-3.30 (m, 4H), 3.38 (m, 1H), 7.14 (dd, 1H), 7.23 (s, 1H), 7.32 (dd, 1H), 7.55 (d, 1H).

#### 15 Example 126

N-(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide hydrochloride salt



To a solution of 3-[6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine (Preparation 8, 1.00 g, 3.26 mmol) in acetone (5 ml) at 0 °C was added methanesulfonyl chloride (0.28 ml, 3.58 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration to afford the title compound as a white crystalline solid (1.19 g, 87%).

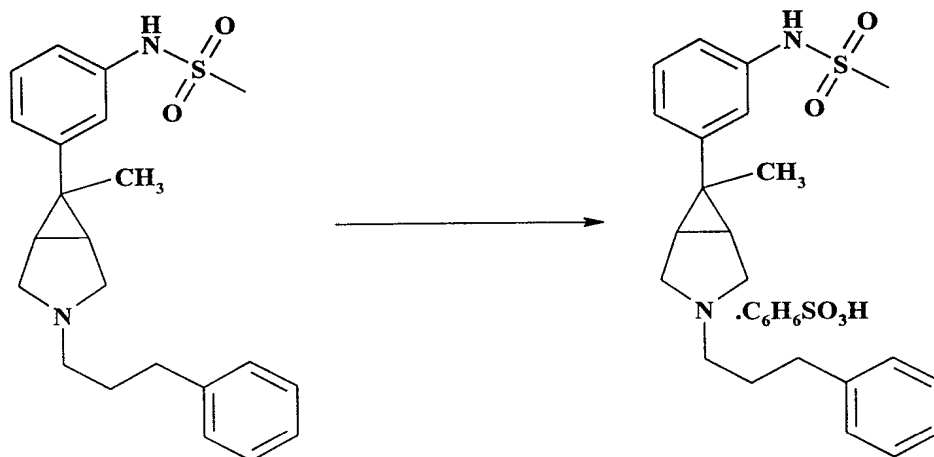
Melting point 212-214 °C.

MS (APCI):  $M/Z$  ( $MH^+$ ) 385.8;  $C_{22}H_{28}N_2O_2S + H$  requires 385.2.

10

#### Example 127

*N*-(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide benzenesulfonate salt



15

A solution of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Example 1, 53.88 g, 0.14 mol) in 2-butanone (480 ml) was heated under reflux. To the solution was added a solution of benzenesulfonic acid (22.17 g, 0.14 mol) in 2-butanone (50 ml) and the reaction mixture was heated under reflux  
5 for 30 min before cooling to 10 °C over a 2 h period. The resulting precipitate was collected by filtration to afford the title compound as a beige crystalline solid (73.55 g, 97%).

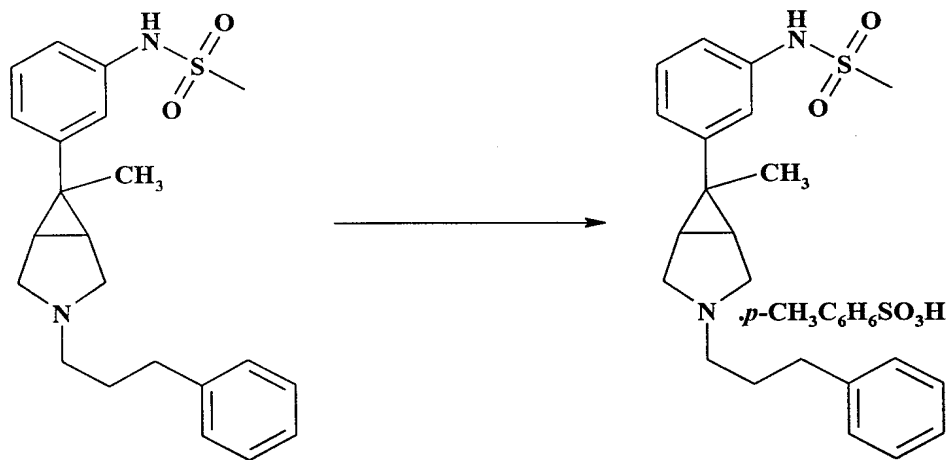
Melting point 166-168 °C.

MS (APCI) : M/Z (MH<sup>+</sup>) 385.7; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 385.2.

10

#### Example 128

*N*-(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide *para*-toluenesulfonate salt



15

A solution of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Example 1, 25.00 g, 65 mmol) in ethyl acetate (250 ml) was heated under reflux. To the solution was added *para*-toluenesulfonic acid (12.36 g, 72  
20 mmol) and the reaction mixture was heated under reflux for 60 min before cooling to 10 °C over a 2 h period. The resulting precipitate was collected by filtration to afford the title compound as a white solid (35.46 g, 95%).

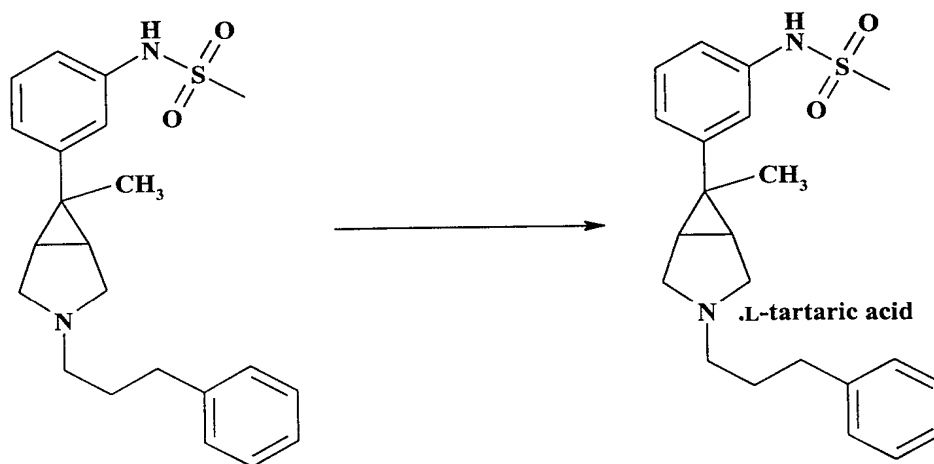
Melting point 182-184 °C.

MS (APCI) : M/Z (MH<sup>+</sup>) 385.3; C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 385.2.

Example 129

*N*-(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide L-tartrate salt

5



A solution of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Example 1, 2.00 g, 5.2 mmol) in Industrial Methylated  
 10 Spirits (20 ml) was heated under reflux. To the solution was added L-tartaric acid (0.86 g, 5.8 mmol) and the reaction mixture was heated under reflux for 30 min before cooling to 10 °C over a 2 h period. The resulting precipitate was collected by filtration to afford the title compound as a white solid (1.40 g, 50%).

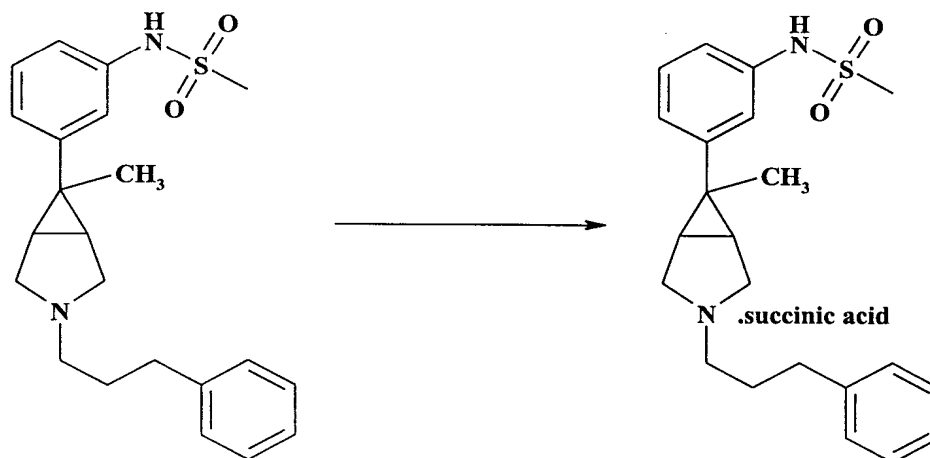
Melting point 162-164 °C.

15 MS (APCI):  $M/Z$  ( $MH^+$ ) 385.5;  $C_{22}H_{28}N_2O_2S + H$  requires 385.2.

Example 130

*N*-(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide succinate salt

20



A solution of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Example 1, 2.00 g, 5.2 mmol) in Industrial Methy-  
 5 lated Spirits (20 ml) was heated under reflux. To the solution was added succinic acid (0.68 g, 5.8 mmol) and the reaction mixture was heated under reflux for 30 min before cooling to 10 °C over a 2 h period. The resulting precipitate was collected by filtration to afford the title compound as a white solid (1.42 g, 54%).

Melting point 162-164 °C.

10 MS (APCI) :  $M/Z$  ( $MH^+$ ) 385.4;  $C_{22}H_{28}N_2O_2S + H$  requires 385.2.

### Example 131

Formulation of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

15

A composition suitable for intravenous administration is as follows:-

<i>N</i> -(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide acetate salt (Example 2)	45 mg
--	-------

Dimethylsulfoxide	2.02 ml
-------------------	---------

20 0.9% w : v Aqueous sodium chloride solution	42.98 ml
--	----------

### Example 132

Formulation of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

A composition suitable for oral capsule administration is as follows:-

	<i>N</i> -(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide hydrochloride salt (Example 126)	59.4	mg
5	Tetraglycol	2.715	ml
	Polyethyleneglycol 400	2.715	ml

A suspension of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide hydrochloride salt (Example 126) in 50 : 50 tetraglycol :  
 10 polyethylene glycol 400 was placed on a Denley Spiromix 5™ overnight to afford a solution. The solution was placed in a hard gelatin capsule shell, size 0, and the capsule lid was placed on the capsule body and sealed tight.

#### Example 133

15 Formulation of *N*-(3-{6-methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

A composition suitable for oral gavage administration is as follows:-

	<i>N</i> -(3-{6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide <i>para</i> -toluenesulfonate salt (Example 128)	140	mg
20	Propylene glycol	70	ml

#### Example 134

25 Formulation of *N*-(3-{3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

A composition suitable for oral gavage administration is as follows:-

	<i>N</i> -(3-{3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)-methanesulfonamide hydrochloride salt (Example 6)	80	mg
30	Propylene glycol	40	ml

#### Example 135

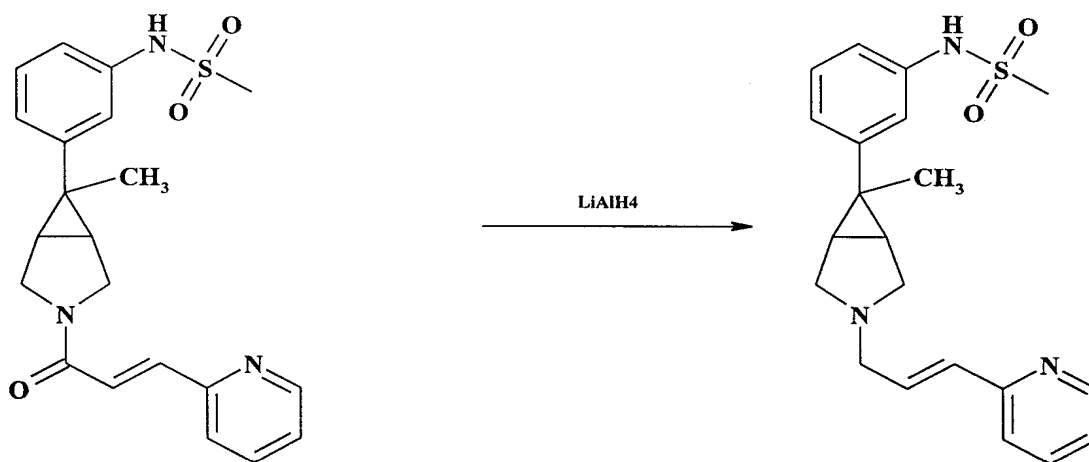
Formulation of *N*-(3-{3-(3-cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)ethanesulfonamide

A composition suitable for oral gavage administration is as follows:-

- |   |   |       |
|---|---|-------|
| 5 | <i>N</i> -(3-{3-(3-Cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)ethanesulfonamide hydrochloride salt (Example 5) | 70 mg |
|   | Water   | 35 ml |

Example 136

- 10 *N*-(3-{6-Methyl-3-[(*E*)-3-(2-pyridinyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



- 15 To a solution of *N*-(3-{6-methyl-3-[(*E*)-3-(2-pyridinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 141, 172 mg, 0.43 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at room temperature was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) and the reaction mixture was stirred at room
- 20 temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (0.5 ml), sodium carbonate (0.5 g) and ethyl acetate (5 ml). The reaction mixture was left to stir for 1 h 30 min, filtered, solid washed with methanol (5 ml) and combined filtrate concentrated using a stream of nitrogen to afford 215 mg of a pale brown oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel

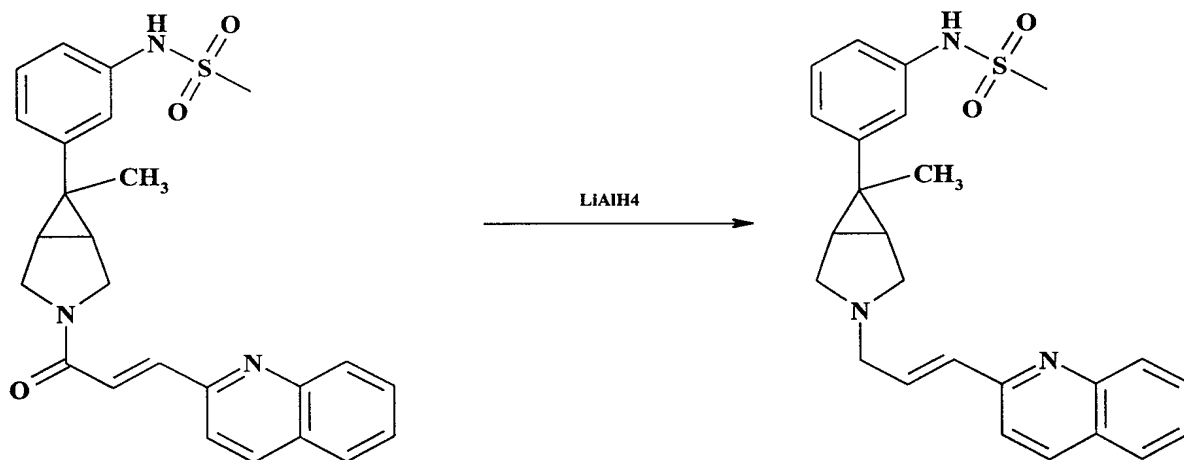
(40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (300 : 8 : 1) to afford the title compound as a pale brown oil (78 mg, 47%).

NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.78 (br. s, 2H), 2.90 (br. d, 2H), 3.00 (s, 3H), 3.12 (d, 2H), 3.37 (d, 2H), 6.60-6.70 (m, 2H), 7.00 (d, 1H), 7.05-7.15 (m, 3H), 7.20-7.35 (m, 2H), 7.62 (dd, 1H), 8.57 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 384.3; C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 384.2.

### Example 137

N-(3-{6-Methyl-3-[(E)-3-(2-quinolinyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of N-(3-{6-methyl-3-[(E)-3-(2-quinolinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 142, 206 mg, 0.46 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at room temperature was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) and the reaction mixture was stirred at room temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (0.5 ml), sodium carbonate (0.5 g) and ethyl acetate (5 ml). The reaction mixture was left to stir for 1 h 30 min, filtered, solid washed with methanol (5 ml) and combined filtrate concentrated using a stream of nitrogen to afford 221 mg of a pale brown oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (300 : 8 : 1) to afford the title compound as a dark yellow oil (84 mg, 42%).



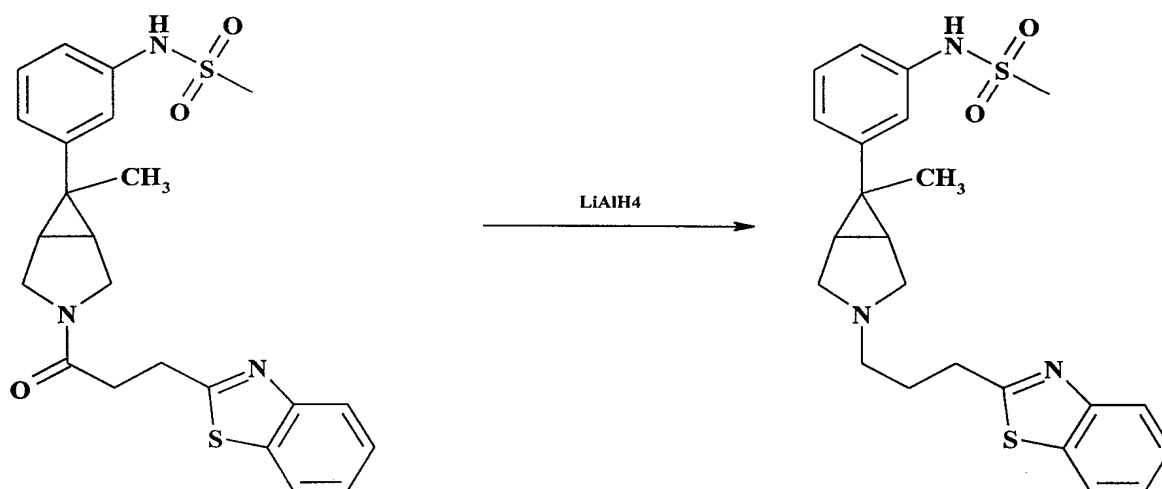
NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.79 (br. s, 2H), 2.92 (d, 2H), 3.00 (s, 3H), 3.13 (d, 2H), 3.42 (d, 2H), 6.80-6.88 (m, 2H), 7.00 (d, 1H), 7.05-7.10 (m, 2H), 7.23 (m, 1H), 7.47 (dd, 1H), 7.56 (d, 1H), 7.68 (dd, 1H), 7.75 (d, 1H), 8.05 (d, 1H), 8.10 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 434.3; C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 434.2.

5

### Example 138

N-(3-{3-[3-(1,3-Benzothiazol-2-yl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



10

To a solution of *N*-(3-{3-[3-(1,3-benzothiazol-2-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 143, 228 mg, 0.50 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at room temperature was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) and the reaction mixture was stirred at room temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (0.5 ml), sodium carbonate (0.5 g) and ethyl acetate (5 ml). The reaction mixture was left to stir for 1 h 30 min, filtered, solid washed with methanol (5 ml) and combined filtrate concentrated using a stream of nitrogen to afford 650 mg of a pale brown oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (300 : 8 : 1) to afford the title compound as a yellow oil (198 mg, 90%).

20

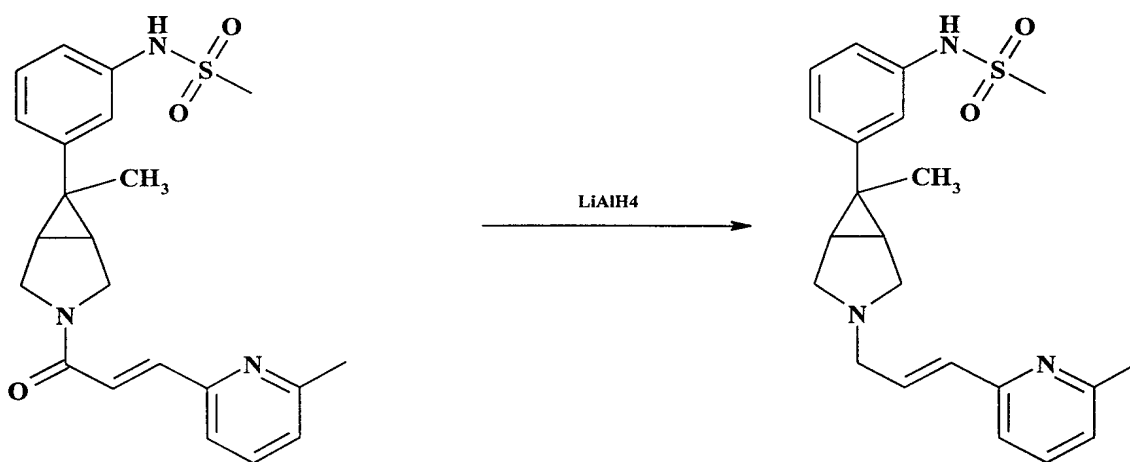
NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.76 (m, 2H), 2.02 (dd, 2H), 2.60 (dd, 2H), 2.80 (br. d, 2H), 3.00 (s, 3H), 3.10 (d, 2H), 3.16 (dd, 2H), 7.00 (d, 1H), 7.05-7.10 (m, 2H), 7.23 (m, 1H), 7.35 (dd, 1H), 7.45 (dd, 1H), 7.83 (d, 1H), 7.96 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 442.3; C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 442.2.

5

### Example 139

N-(3-{6-Methyl-3-[(E)-3-(6-methyl-2-pyridinyl)-2-propenyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



10

To a solution of *N*-(3-{6-methyl-3-[(*E*)-3-(6-methyl-2-pyridinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 144, 191 mg, 0.46 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at room temperature was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) and the reaction mixture was stirred at room temperature for 2 h. The rapidly stirred reaction mixture was treated sequentially with water (0.5 ml), sodium carbonate (0.5 g) and ethyl acetate (5 ml). The reaction mixture was left to stir for 1 h 30 min, filtered, solid washed with methanol (5 ml) and combined filtrate concentrated using a stream of nitrogen to afford 221 mg of a dark yellow oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (300 : 8 : 1) to afford the title compound as a pale brown oil (102 mg, 56%).

20

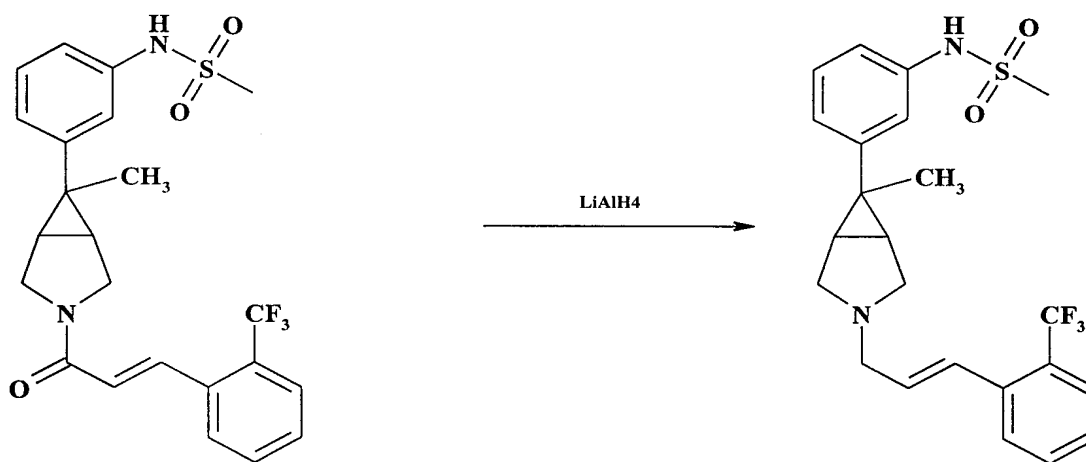
NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.78 (br. s, 2H), 2.55 (s, 3H), 2.90 (d, 2H), 3.00 (s, 3H), 3.08 (d, 2H), 3.35 (d, 2H), 6.63-6.69 (m, 2H), 6.97-7.03 (m, 2H), 7.05-7.10 (m, 2H), 7.15 (d, 1H), 7.23 (m, 1H), 7.53 (dd, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 398.3; C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S + H requires 398.2.

5

#### Example 140

N-[3-(6-Methyl-3-{{(E)-3-[2-(trifluoromethyl)phenyl]-2-propenyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



10

To a solution of *N*-[3-(6-methyl-3-{{(E)-3-[2-(trifluoromethyl)phenyl]-2-propenyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 145, 240 mg, 0.52 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at room temperature was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.55 ml, 0.55 mmol) and the reaction mixture was stirred at room temperature for 5 h. A further addition of lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.50 ml, 0.50 mmol) was made dropwise and the reaction mixture was left a further 30 min. The rapidly stirred reaction mixture was treated sequentially with water (1.0 ml), sodium carbonate (1.0 g) and ethyl acetate (5 ml). The reaction mixture was left to stir for 1 h 30 min, filtered, solid washed with methanol (5 ml) and combined filtrate concentrated using a stream of nitrogen to afford 689 mg of a pale yellow oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel

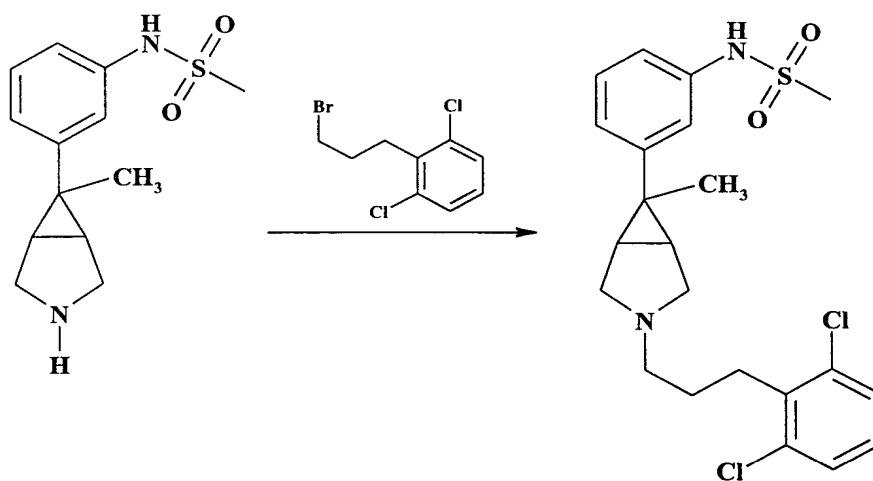
(40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (600 : 8 : 1) to afford the title compound as a pale yellow oil (77 mg, 33%).

NMR (CDCl<sub>3</sub>, selected data) : 1.58 (s, 3H), 1.76 (m, 2H), 2.55 (dd, 1H), 2.80 (dd, 1H), 2.88 (d, 1H), 3.00 (s, 3H), 3.07-3.13 (m, 2H), 3.33 (d, 1H), 6.22 (ddd, 1H), 6.95 (d, 1H),  
 5 7.02 (d, 1H), 7.05-7.12 (m, 2H), 7.24-7.28 (m, 2H), 7.33 (dd, 1H), 7.49 (dd, 1H), 7.62 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 451.4; C<sub>23</sub>H<sub>25</sub><sup>19</sup>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 451.2.

#### Example 141

#### 10 N-(3-{3-[3-(2,6-Dichlorophenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



- 15 To a solution of the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 226 mg, 0.746 mmol) in *N,N*-dimethylformamide (10 ml) was added 2-(3-bromopropyl)-1,3-dichlorobenzene (J. Augstein et al., J. Med. Chem., 1967, 10, 391; 200 mg, 0.746 mmol) and sodium hydrogen carbonate (187 mg 2.238 mmol). The reaction mixture was heated at 80°C for overnight  
 20 before allowing to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was partitioned between water (10 ml) and ethyl acetate (15 ml). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a brown oil (325 mg). The residue was purified by silica (5 g) gel chromatography eluting with

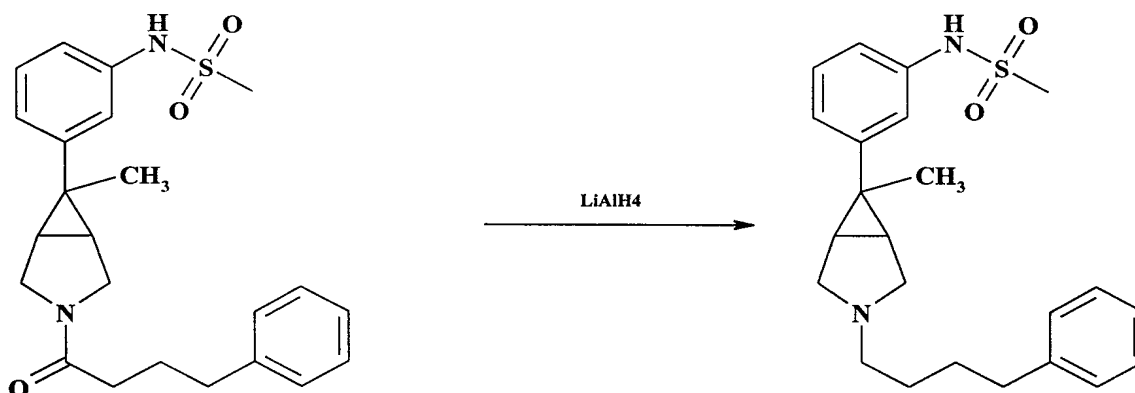
dichloromethane : ethanol : 0.880 ammonia (250 : 8 : 1) to afford the title compound as a pale yellow oil (42 mg, 13%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.58 (s, 3H), 1.65-1.80 (m, 4H), 2.60 (t, 2H), 2.85 (br. m, 2H), 2.97 (d, 2H), 3.00 (s, 3H), 3.15 (d, 2H), 7.00-7.15 (m, 4H), 7.22-7.30 (m, 3H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 453; C<sub>22</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S + H requires 453.

#### Example 142

N-{3-[6-Methyl-3-(4-phenylbutyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



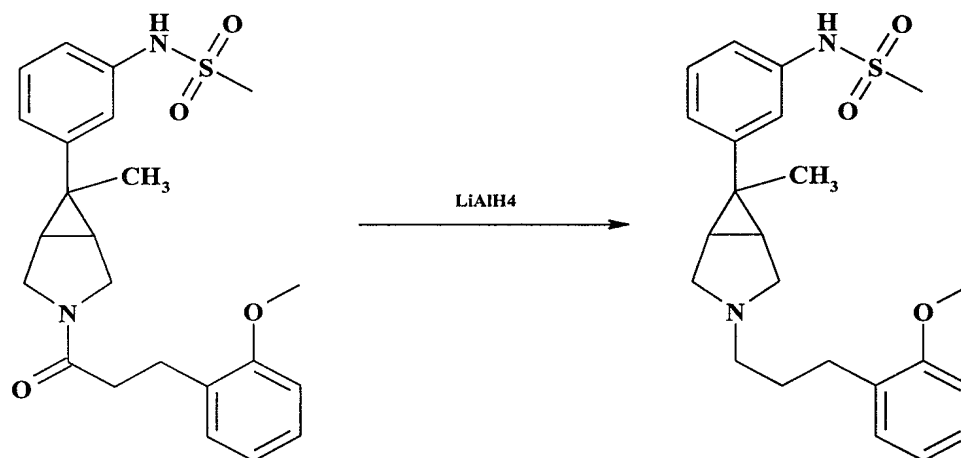
To a solution of N-{3-[6-methyl-3-(4-phenylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Preparation 146, 100 mg, 0.24 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.48 ml, 0.48 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (0.48 ml), sodium carbonate (500 mg) and ethyl acetate (10 ml). The reaction mixture was left to stir for 15 min, filtered, solid washed with ethyl acetate (10 ml) and combined filtrate concentrated *in vacuo* to afford 102 mg of a pale yellow oil. The residue was purified by silica (4 g) gel chromatography eluting with dichloromethane : ethanol : 0.880 ammonia (250 : 8 : 1) to afford the title compound as a pale yellow oil (80 mg, 84%).

NMR (CDCl<sub>3</sub>, selected data) : 1.45-1.58 (m, 5H), 1.66 (dd, 2H), 1.75 (m, 2H), 2.48 (t, 2H), 2.63 (t, 2H), 2.80 (br. d, 2H), 2.95-3.00 (m, 5H), 7.00-7.12 (m, 3H), 7.15-7.32 (m, 6H).

MS (electrospray) :  $M/Z$  ( $MH^+$ ) 398.8;  $C_{23}H_{30}N_2O_2S + H$  requires 399.2.

### Example 143

*N*-(3-{3-[3-(2-Methoxyphenyl)propyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



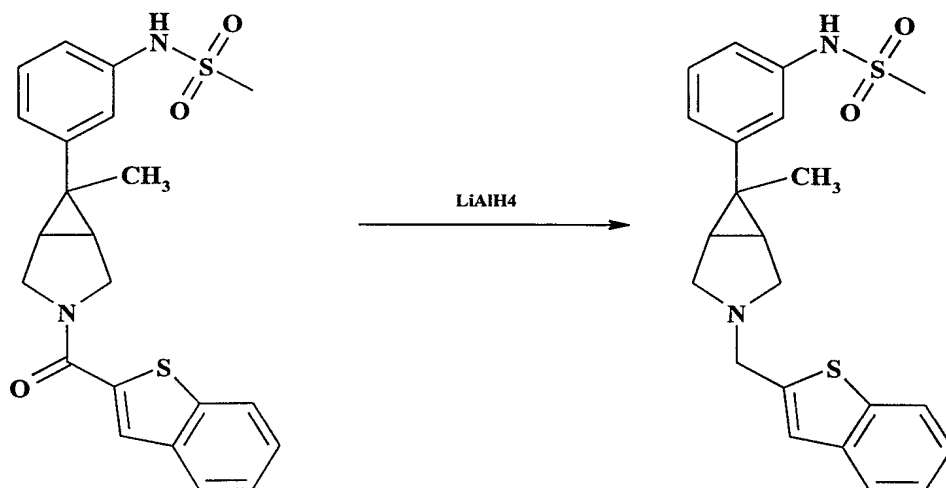
To a solution of *N*-(3-{3-[3-(2-methoxyphenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide (Preparation 147, 100 mg, 0.234 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.47 ml, 0.47 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (0.47 ml), sodium carbonate (500 mg) and ethyl acetate (10 ml). The reaction mixture was left to stir for 15 min, filtered, solid washed with ethyl acetate (10 ml) and combined filtrate concentrated *in vacuo* to afford 103 mg of a pale yellow oil. The residue was purified by silica (4 g) gel chromatography eluting with dichloromethane : ethanol : 0.880 ammonia (250 : 8 : 1) to afford the title compound as a colourless oil (86 mg, 89%).

NMR ( $CDCl_3$ , selected data) : 1.55 (s, 3H), 1.70-1.85 (m, 4H), 2.50 (t, 2H), 2.65 (t, 2H), 2.80 (m, 2H), 3.00-3.10 (m, 5H), 3.80 (s, 3H), 6.80-6.95 (m, 2H), 7.00-7.30 (m, 6H).

MS (thermospray) :  $M/Z$  ( $MH^+$ ) 415.1;  $C_{23}H_{30}N_2O_3S + H$  requires 415.2.

### Example 144

*N*-{3-[3-(1-Benzothiophen-2-ylmethyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



5

To a solution of *N*-{3-[3-(1-benzothiophen-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide (Preparation 148, 100 mg, 0.235 mmol) in anhydrous tetrahydrofuran (2.5 ml) under a nitrogen atmosphere at 0 °C was added dropwise lithium aluminium hydride (1.0M solution in tetrahydrofuran, 0.47 ml, 0.47 mmol) and the reaction mixture was stirred at room temperature overnight. The rapidly stirred reaction mixture was treated sequentially with water (0.47 ml), sodium carbonate (500 mg) and ethyl acetate (10 ml). The reaction mixture was left to stir for 15 min, filtered, solid washed with ethyl acetate (10 ml) and combined filtrate concentrated *in vacuo* to afford 104 mg of a light yellow oil. The residue was purified by silica (4 g) gel chromatography eluting with hexane : ethyl acetate : 0.880 ammonia (50 : 50 : 1) to afford the title compound as a colourless oil (74 mg, 76%).

15

NMR ( $\text{CDCl}_3$ , selected data) : 1.60 (s, 3H), 1.80 (br. s, 2H), 2.88 (m, 2H), 3.00 (s, 3H), 3.98 (br. s, 2H), 7.00-7.20 (m, 3H), 7.25-7.40 (m, 4H), 7.70 (d, 1H), 7.80 (d, 1H).

MS (electrospray) :  $\text{M/Z (MH}^+)$  413.2;  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2 + \text{H}$  requires 413.1.

20

Preparation 1Ethyl (E)-3-(3-nitrophenyl)-2-butenolate

To a solution of sodium hydride (60% dispersion in oil, 20 g, 0.5 mol) in tetrahydrofuran (1 l) stirred at -10°C under nitrogen was added dropwise over 30 minutes triethylphosphonoacetate (112 g, 0.5 mol). A further portion of sodium hydride (60% dispersion in oil, 20 g, 0.5 mol) and tetrahydrofuran (1 l) was added followed by dropwise addition of triethylphosphonoacetate (112 g, 0.5 mol) over 30 minutes. 3-Nitroacetophenone (165 g, 1 mol) was added portionwise such that the temperature was maintained below 10°C. The mixture was allowed to warm to room temperature and was stirred for 1 h. Water (2 l) was added, and the mixture was extracted with diethyl ether (2 x 1 l). The combined extracts were washed with water (1 l), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was recrystallised from isopropanol to give a first crop of the title compound as a white solid (90 g, 38%).

mp 43 - 44°C

NMR (CDCl<sub>3</sub>) δ: 1.34 (t, 3H), 2.60 (s, 3H), 4.25 (q, 2H), 6.20 (s, 1H), 7.56 (t, 1H), 7.80 (d, 1H), 8.22 (d, 1H), 8.33 (s, 1H)

MS (thermospray): M/Z [MNH<sub>4</sub><sup>+</sup>] 253.1; C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub> + NH<sub>4</sub> requires 253.1

Preparation 2(E)-3-(3-Nitrophenyl)-2-buten-1-ol

To a solution of ethyl (E)-3-(3-nitrophenyl)-2-butenolate (Preparation 1, 102 g, 0.43 mol) in toluene (1400 ml) at -10°C under nitrogen was added dropwise over 3 h diisobutylaluminium hydride (1.0 M in toluene, 1 l), then the mixture was stirred at 0°C for 1 h. Water (400 ml) was carefully added, followed by sodium hydrogen carbonate (300 g). The resulting slurry was vigorously stirred for 10 min, then ethyl acetate (2 l) was added, and the mixture stirred for 1 h. The mixture was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give the title compound as a pale brown oil (81 g, 97%).

NMR (CDCl<sub>3</sub>) δ: 2.11 (s, 3H), 4.41 (d, 2H), 6.08 (t, 1H), 7.48 (t, 1H), 7.72 (d, 1H), 8.10 (d, 1H), 8.25 (s, 1H).

MS (thermospray) : M/Z [MH<sup>+</sup>] 194.1; C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub> + H requires 194.1



Preparation 31-[(E)-3-Chloro-1-methyl-1-propenyl]-3-nitrobenzene

5 To a solution of N-chlorosuccinimide (52.3 g, 0.39 mol) in dichloromethane (800 ml) at 0 °C was added dropwise over 1 h dimethylsulfide (27.9ml, 0.38 mol). To the mixture was added dropwise over 30 min at 0°C a solution of (E)-3-(3-nitrophenyl)-2-buten-1-ol (Preparation 2, 72g, 0.373 mol) in dichloromethane (200 ml). The mixture was warmed to room temperature over 1 h, then poured onto brine (500 ml). The layers were  
10 separated, and the aqueous layer extracted with ether (500 ml). The organic extracts were combined, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography, eluting with 10:1 hexane/ethyl acetate, then as a gradient up to 4:1 hexane/ethyl acetate. Appropriate fractions were combined and concentrated *in vacuo* to give the title compound as a very pale yellow solid (69 g,  
15 88%).

mp 46 - 47°C

NMR (CDCl<sub>3</sub>) δ: 2.20 (s, 3H), 4.27 (d, 2H) 6.10 (t, 1H), 7.52 (t, 1H), 7.73 (d, 1H), 8.13 (d, 1H), 8.26 (s, 1H).

20 Preparation 4

1-[(E)-3-Bromo-1-methyl-1-propenyl]-3-nitrobenzene

To a solution of triphenylphosphine (5.15 g, 19.7 mmol) in acetonitrile (140 ml) was added dropwise over 5 minutes a solution of bromine (3.15 g, 19.7 mmol) in acetonitrile  
25 (5 ml) at a rate such that the temperature did not exceed -10°C. The mixture was allowed to warm to room temperature, then to this was added a solution of (E)-3-(3-nitrophenyl)-2-buten-1-ol (Preparation 2, 4 g, 20.7 mmol) in acetonitrile (5 ml). The mixture was warmed gently to 65°C for 1 h, cooled to room temperature and then poured onto diethyl ether (50 ml). The mixture was concentrated *in vacuo*, then diethyl ether  
30 (200 ml) was added. The mixture was filtered, concentrated again *in vacuo* and the residue purified by silica column (300 g) chromatography, eluting with 3:1 hexane/dichloromethane then 1:1 hexane/dichloromethane. Appropriate fractions were

combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (4 g, 75%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 2.20 (s, 3H), 4.20 (d, 2H) 6.20 (t, 1H), 7.51 (t, 1H), 7.73 (d, 1H), 8.13 (d, 1H), 8.26 (s, 1H).

5

#### Preparation 5

#### Ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)cyclopropane-carboxylate

- 10 To a solution of 1-[(*E*)-3-chloro-1-methyl-1-propenyl]-3-nitrobenzene (Preparation 3, 36 g, 0.17 mol) in dichloromethane (50 ml) was added rhodium (II) acetate dimer (1 g, 2.3 mmol). To the mixture was added dropwise at room temperature over 8 h a solution of ethyl diazoacetate (50 ml, 54.25 g, 0.475 mol) in dichloromethane (50ml), then the mixture was stirred at room temperature for 16 h. To the mixture was added dropwise at
- 15 room temperature over 7 h a further solution of ethyl diazoacetate (50 ml, 54.25 g, 0.475 mol) in dichloromethane (50ml), then the mixture was stirred at room temperature for a further 16 h. The mixture was concentrated *in vacuo* and the residue purified by silica column (1 kg) chromatography, eluting with 1:1 hexane/dichloromethane then dichloromethane. Product-containing fractions were combined and concentrated *in*
- 20 *vacuo*, then concentrated under a stream of nitrogen for 16 h. The residue was purified further by silica column (2 kg) chromatography, eluting with 1:1 hexane/dichloromethane then dichloromethane. Product containing fractions were combined and concentrated *in vacuo*, to give the title compound as a very pale yellow oil (14.2 g, 29%).
- 25 NMR (CDCl<sub>3</sub>)  $\delta$ : 1.34 (t, 3H), 1.60 (s, 3H), 2.01 (m, 1H), 2.20 (d, 1H), 4.03 (dd, 1H), 4.15 - 4.27 (m, 3H), 7.50 (t, 1H), 7.69 (d, 1H), 8.10 (d, 1H), 8.19 (s, 1H)

#### Preparation 6

#### Ethyl 3-(bromomethyl)-2-methyl-2-(3-nitrophenyl) cyclopropane carboxylate

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To a solution of 1-[(E)-3-bromo-1-methyl-1-propenyl]-3-nitrobenzene (Preparation 4, 4 g, 15.6 mmol) in dichloromethane (5 ml) was added rhodium (II) acetate dimer (100 mg, 0.22 mmol). To the mixture was added dropwise at room temperature over 4.5 h a solution of ethyl diazoacetate (3.1 ml, 2.84g, 25 mmol) in dichloromethane (15 ml). The mixture was filtered, concentrated *in vacuo*, and the residue purified by silica column (100 g) chromatography, eluting with 2:1 hexane/dichloromethane then dichloromethane. Product-containing fractions were combined and concentrated *in vacuo*, then purified further by preparative HPLC (Condition 1). Combination and evaporation of appropriate fractions gave the title compound as a colourless oil (0.5 g, 11%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.34 (t, 3H), 1.60 (s, 3H), 2.10 (m, 1H), 2.22 (d, 1H), 3.88 (dd, 1H), 4.06 (t, 1H), 4.23 (m, 2H), 7.50 (t, 1H), 7.72 (d, 1H), 8.12 (d, 1H), 8.22 (s, 1H).

#### Preparation 7

##### 6-Methyl-6-(3-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)-cyclopropane carboxylate (Preparation 5, 14.4 g, 48.6 mmol), in N,N-dimethylformamide (120 ml) was added sodium hydrogen carbonate (12 g, 143 mmol) and 3-phenylpropylamine (38.8 g, 41 ml, 290 mmol). The mixture was heated to 150°C for 7 h, then cooled to room temperature and poured onto water (1000 ml). The mixture was extracted with diethyl ether (2 x 500 ml), and the combined extracts were washed with water (2 x 250 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (1000 g) column chromatography eluting with dichloromethane then dichloromethane/ethyl acetate 4:1. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (6.2 g, 36%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.37 (s, 3H), 1.88 (p, 2H), 2.16 (t, 1H), 2.36 (d, 1H), 2.66 (t, 2H), 3.23 (m, 1H), 3.38 (m, 2H), 3.70 (m, 1H), 7.20 (m, 3H), 7.27 (m, 2H), 7.48 (t, 1H), 7.64 (d, 1H), 8.07 (d, 1H), 8.16 (s, 1H)

MS (thermospray) : M/Z [MH<sup>+</sup>] 351.1; C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> + H requires 351.2

#### Preparation 8

##### 3-[6-Methyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine

Method A: To a solution of 6-methyl-6-(3-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 7, 6.2 g, 17.71 mmol) in anhydrous tetrahydrofuran (200 ml) at room temperature under nitrogen, was added dropwise a solution of lithium aluminium hydride (1.0M in tetrahydrofuran, 100 ml, 100 mmol), then the mixture was gently refluxed for 4 h. The mixture was cooled, then quenched by the careful addition of water (200 ml). The pH of the mixture was adjusted to 4 by the addition of dilute hydrochloric acid, then adjusted to pH 10 by the addition of dilute sodium hydroxide solution. The mixture was extracted with ethyl acetate (2 x 200 ml), and the combined extracts were washed with water (100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give 5.2 g of a yellow oil. This was dissolved in ethanol (200 ml), Raney nickel (300 mg) was added and the mixture was placed under an atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 60°C for 18 h. The mixture was cooled, filtered through Arbocel™, and concentrated *in vacuo* to give the title compound as a very pale yellow oil (4.6 g, 85%).

Or Method B: (i) To a stirred solution of 6-methyl-6-(3-nitrophenyl)-3-(3-phenylpropyl)azabicyclo[3.1.0]hexane-2,4-dione (Preparation 136, 15.0 g, 41.2 mmol) in tetrahydrofuran (60 ml) under nitrogen was added sodium borohydride (3.27 g, 86.4 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to between 0 °C and 5 °C and borontrifluoride diethyletherate (16.36 g, 115 mmol) was added. The reaction mixture was allowed to warm to room temperature over 2 h before being heated under reflux for a further 2 h. The reaction mixture was cooled to between 0 °C and 5 °C and an aqueous solution of piperazine (20.92 g in 120 ml) was added. The reaction mixture was then heated under reflux for 18 h. The tetrahydrofuran was removed by distillation and the reaction mixture was allowed to cool to 50 °C. Ethyl acetate (90 ml) was added and the resulting biphasic mixture was allowed to cool to room temperature. The phases were separated and the organic extract was washed water (3 x 60 ml) to afford a solution of 6-(3-nitrophenyl)-6-methyl-3-(3-phenylpropyl)azabicyclo[3.1.0]hexane in ethyl acetate.

(ii) To the reaction mixture was added 5% palladium on charcoal (Johnsson Matthey type 87, 1.5 g) and the reaction mixture was placed under an atmosphere of hydrogen (60

psi) at 25 °C for 16 h. The catalyst was removed by filtration through Celite™ and the filtrate was concentrated *in vacuo* to afford the title compound as a yellow oil which crystallised on standing (11.09 g, 88 %).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 1.52 (s, 3H), 1.71-1.78 (m, 4H), 2.47 (t, 2H), 2.66 (t, 2H), 2.79 (d, 2H), 2.99 (d, 2H), 3.59 (s, 2H), 6.49 (d, 1H), 6.60 (s, 1H), 6.65 (d, 1H), 7.06 (t, 1H), 7.15-7.20 (m, 2H), 7.20-7.30 (m, 3H).

MS (APCI): M/Z [MH<sup>+</sup>] 307.3; C<sub>21</sub>H<sub>26</sub>N<sub>2</sub> + H requires 307.2

### Preparation 9

#### 10 3-(3-Cyclohexylpropyl)-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one

A solution of ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)cyclopropane carboxylate (Preparation 5, 1 g, 3.36 mmol) in 3-cyclohexylpropylamine ([Preparation - Eur. J. Med. Chem. (1992), 27, 321-330], 2.9 g, 20.5 mmol) was heated to 160°C for 16 h.

15 The mixture was cooled, 2N hydrochloric acid solution (20 ml) was added and the mixture was extracted with dichloromethane (3 x 20 ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (200 g) column chromatography eluting with dichloromethane then diethyl ether. Appropriate fractions were combined and concentrated *in vacuo* to give the title  
20 compound as an amber oil (870 mg, 73%).

NMR (CDCl<sub>3</sub>) δ: 0.90 (m, 2H), 1.22 (m, 6H), 1.38 (s, 3H), 1.47-1.60 (m, 2H), 1.60-1.75 (m, 5H), 2.14 (t, 1H), 2.37 (d, 1H), 3.08-3.30 (m, 2H), 3.36 (d, 1H), 3.73 (dd, 1H), 7.48 (t, 1H), 7.64 (d, 1H), 8.08 (d, 1H), 8.16 (s, 1H)

MS (thermospray) : M/Z [MH<sup>+</sup>] 357.1; C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> + H requires 357.2

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### Preparation 10

#### 3-[3-(3-Cyclohexylpropyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]aniline

To a solution of 3-(3-cyclohexylpropyl)-6-methyl-6-(3-nitrophenyl)-3-azabicyclo  
30 [3.1.0]hexan-2-one (Preparation 9, 56 mg, 0.16 mmol) in anhydrous tetrahydrofuran (2.5 ml) at room temperature under nitrogen was added dropwise a solution of lithium aluminium hydride (1.0M in tetrahydrofuran, 0.8 ml, 0.8 mmol), then the mixture was

gently refluxed for 4.5 h. The mixture was cooled, then quenched by the careful addition of water (30 ml). The pH of the mixture was adjusted to 1 by the addition of dilute hydrochloric acid, then adjusted to pH 10 by the addition of dilute sodium hydroxide solution. The mixture was extracted with ethyl acetate (40 ml) and the organic extract  
5 was washed with water (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give 50 mg of a yellow oil. This was dissolved in ethanol (6 ml), and Raney nickel (50 mg) was added and the mixture was placed under an atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 60°C for 7 h. The mixture was cooled, filtered through Arbocel™, and concentrated *in vacuo*, to give the title compound as a very pale yellow oil (50 mg,  
10 99%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (m, 2H), 1.06-1.31 (m, 6H), 1.43 (s, 3H), 1.58-1.76 (m, 7H), 2.02 (s, 2H), 2.70 (t, 2H), 2.97 (d, 2H), 3.42 (m, 2H), 6.40-6.63 (m, 3H), 7.08 (m, 1H)  
MS (thermospray) : M/Z [ $\text{MH}^+$ ] 313.4;  $\text{C}_{21}\text{H}_{32}\text{N}_2 + \text{H}$  requires 313.3

#### 15 Preparation 11

##### 3-Hexyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)cyclopropane carboxylate (Preparation 5, 20 g, 67.2 mmol) in hexylamine (36 ml, 270 mmol) was  
20 added sodium hydrogen carbonate (5.64 g, 67.2 mmol), and the mixture was heated at 100°C for 16 h. The mixture was cooled, diluted with water (80 ml) and extracted with dichloromethane (3 x 150 ml). The combined extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography, eluting with a gradient of 2:1 to 1:2 hexane/ethyl acetate. Appropriate fractions were  
25 combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (14.2 g, 67%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (t, 3H), 1.23-1.38 (m, 6H), 1.38 (s, 3H), 1.46-1.60 (m, 2H), 2.17 (t, 1H), 2.37 (d, 1H), 3.11-3.40 (m, 3H), 3.71 (dd, 1H), 7.49 (t, 1H), 7.65 (m, 1H), 8.08 (d, 1H), 8.15 (s, 1H)

30 MS (APCI) : M/Z [ $\text{MH}^+$ ] 317.5;  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}$  requires 317.2

#### Preparation 12

3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine

To a solution of 3-hexyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 11, 10.7 g, 33.86 mmol) in tetrahydrofuran (500 ml) under nitrogen, was added dropwise over 1 h at room temperature a 1.0 M solution of lithium aluminium hydride in tetrahydrofuran (100 ml, 100 mmol). The mixture was heated to 50 °C for 2 h, then cooled to room temperature. Water (50 ml) was carefully added, and the mixture was stirred for 1 h, before the tetrahydrofuran was removed *in vacuo*. The aqueous residue was acidified by the addition of 2N hydrochloric acid (20 ml) and then basified with the addition of 2N sodium hydroxide solution (25 ml). The mixture was extracted with ethyl acetate (3 x 250ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was dissolved in ethanol (450 ml), Raney nickel (500 mg) was added, and the mixture was placed under an atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 50°C for 24 hours. The mixture was filtered through Celite™, and concentrated *in vacuo*. The residue was purified by silica column chromatography, eluting with 80:20:2 ethyl acetate/methanol/ammonia solution (0.880). Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil (3.3 g, 36%).

NMR (CDCl<sub>3</sub>) δ: 0.90 (t, 3H), 1.30 (m, 6H), 1.42 (m, 2H), 1.46 (s, 3H), 1.74 (s, 2H), 2.43 (t, 2H), 2.82 (d, 2H), 2.93 (d, 2H), 6.48 (d, 1H), 6.59 (s, 1H), 6.65 (d, 1H), 7.05 (t, 1H)

MS (thermospray) : M/Z [MH<sup>+</sup>] 273.4; C<sub>18</sub>H<sub>28</sub>N<sub>2</sub> + H requires 273.2

Preparation 1325 Ethyl (E)-3-(3-nitrophenyl)-2-pentenoate

To a solution of sodium hydride (60% dispersion in oil, 40 g, 1.0 mol) in tetrahydrofuran (2 l) stirred at -10°C under nitrogen was added dropwise over 30 minutes triethylphosphonoacetate (224 g, 1.0 mol). 3-Nitropropiophenone (180 g, 1 mol) was added portionwise such that the temperature was maintained below 10°C. The mixture was allowed to warm to room temperature and was stirred for 18 h. Water (1.5 l) was added, and the mixture was extracted with diethyl ether (2 x 1 l). The combined extracts

were washed with water (1 l), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* and the residue was purified by silica column (4 x 2 kg) chromatography eluting with 12:1 hexane/diethyl ether. Appropriate fractions were combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (105 g, 42%).

5 NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.08 (t, 3H), 1.33 (t, 3H), 3.13 (q, 2H), 4.22 (q, 2H), 6.05 (s, 1H), 7.56 (t, 1H), 7.76 (d, 1H), 8.21 (d, 1H), 8.30 (s, 1H)

MS (thermospray):  $m/z$  [ $\text{MH}^+$ ] 250.0;  $\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H}$  requires 250.1

#### Preparation 14

##### 10 (E)-3-(3-Nitrophenyl)-2-penten-1-ol

To a solution of ethyl (E)-3-(3-nitrophenyl)-2-pentenoate (Preparation 13, 105g, 0.43 mol) in toluene (1400 ml) at  $-10^\circ\text{C}$  under nitrogen was added dropwise over 3 h diisobutylaluminium hydride (1.0 M in toluene, 1 l, 1.0 mol), then the mixture was  
15 stirred at  $0^\circ\text{C}$  for 1 hour. Water (400 ml) was carefully added, followed by sodium hydrogen carbonate (700g). The resulting slurry was vigorously stirred for 10 minutes, then ethyl acetate (2 l) was added, and the mixture stirred for 1 h. The mixture was dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to give the title compound as a pale brown oil (80 g, 90%).

20 NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.99 (t, 3H), 2.60 (q, 2H), 4.39 (d, 2H), 5.91 (t, 1H), 7.47 (t, 1H), 7.67 (d, 1H), 8.09 (d, 1H), 8.20 (s, 1H)

#### Preparation 15

##### 1-[(E)-3-Chloro-1-ethyl-1-propenyl]-3-nitrobenzene

25

To a solution of N-chlorosuccinimide (52.3 g, 0.39 mol) in dichloromethane (1.2 l) at  $0^\circ\text{C}$  was added dropwise over 20 minutes dimethylsulfide (27.9 ml, 0.38 mol). To the mixture was added dropwise over 20 minutes at  $0^\circ\text{C}$  a solution of (E)-3-(3-nitrophenyl)-2-penten-1-ol (Preparation 14, 80g, 0.39mol) in dichloromethane (300 ml). The  
30 mixture was warmed to room temperature over 1 h, stirred at room temperature for 16 h, then partitioned between water (2 l) and dichloromethane (1 l). The layers were separated and the organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*.



The residue was purified by silica column chromatography (2 kg), eluting with 10:1 hexane/diethyl ether. Appropriate fractions were combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (54 g, 62%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.33 (t, 3H), 2.63 (q, 2H), 4.27 (d, 2H), 5.94 (t, 1H), 7.52 (t, 1H),  
5 7.69 (d, 1H), 8.15 (d, 1H), 8.23 (s, 1H).

#### Preparation 16

##### Ethyl 3-(chloromethyl)-2-ethyl-2-(3-nitrophenyl)cyclopropanecarboxylate

10 To a solution of 1-[(*E*)-3-chloro-1-ethyl-1-propenyl]-3-nitrobenzene (Preparation 15, 50 g, 0.22 mol) in dichloromethane (40 ml) was added rhodium (II) acetate dimer (2.0 g, 4.6 mmol). To the mixture was added dropwise at room temperature over 6 hours a solution of ethyl diazoacetate (50 ml, 54.25 g, 0.475 mol) in dichloromethane (50 ml), then the mixture stirred at room temperature for 16 hours. To the mixture was added  
15 dropwise at room temperature over 7 hours a solution of ethyl diazoacetate (20 ml, 21.70 g, 0.190 mol) in dichloromethane (20ml), then the mixture was stirred at room temperature for 16 h. The mixture was concentrated *in vacuo* and the residue purified by silica column (1 kg) chromatography, eluting with 1:1 hexane/dichloromethane. Product-containing fractions were combined and concentrated *in vacuo* to give the title  
20 compound as a pale orange oil (10.5 g, 15%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.79 (t, 3H), 1.33 (t, 3H), 1.93-2.11 (m, 3H), 2.20 (d, 1H), 4.04 (dd, 1H), 4.23 (m, 3H), 7.51 (t, 1H), 7.68 (d, 1H), 8.13 (d, 1H), 8.17 (s, 1H)

#### Preparation 17

25 6-Ethyl-6-(3-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 3-(chloromethyl)-2-ethyl-2-(3-nitrophenyl)cyclopropane carboxylate (Preparation 16, 3.5 g, 11.2 mmol), in N,N-dimethylformamide (33 ml) was added sodium hydrogen carbonate (3.3 g, 39 mmol) and 3-phenylpropylamine (10.6 g,  
30 11.2 ml, 79.2 mmol). The mixture was heated to 150°C for 12 h, then cooled to room temperature and partitioned between water (500 ml) and diethyl ether (500 ml). The organic layer was washed successively with water (4 x 250 ml). The aqueous layers

were combined and extracted with diethyl ether (250 ml). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by silica (200 g) column chromatography eluting with dichloromethane. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a very pale yellow oil (1.8 g, 43%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.87 (t, 3H), 1.64 (m, 2H), 1.86 (m, 2H), 2.15 (t, 1H), 2.37 (d, 1H), 2.65 (t, 2H), 3.26 (m, 1H), 3.37 (m, 2H), 3.67 (dd, 1H), 7.20 (m, 3H), 7.27 (m, 2H), 7.48 (t, 1H), 7.67 (d, 1H), 8.08 (d, 1H), 8.17 (s, 1H)

#### 10 Preparation 18

##### 3-[6-Ethyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylamine

To a solution of 6-ethyl-6-(3-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 17, 1.8 g, 4.9 mmol) in anhydrous tetrahydrofuran (60 ml) at room temperature under nitrogen, was added dropwise a solution of lithium aluminium hydride (1.0M in tetrahydrofuran, 32ml, 32mmol) and the mixture was gently refluxed for 6 h. The mixture was cooled, then quenched by carefully pouring into ice cold hydrochloric acid (1N, 400ml). The acidic layer was extracted with diethyl ether (300 ml). The pH of the aqueous layer was adjusted to 10 by the addition of potassium carbonate and extracted with diethyl ether (300 ml). The organic layers were combined, dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to give a yellow oil (1.2 g). This was dissolved in ethanol (60 ml), Raney nickel (120 mg) was added and the mixture was placed under an atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 60°C for 40 h. The mixture was cooled, filtered through Arbocel™, and concentrated *in vacuo* to give the title compound as a very pale yellow oil (1.3 g, 82%).

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.86 (m, 3H), 1.88 (m, 6H), 2.64 (m, 4H), 2.96 (m, 2H), 3.09 (m, 2H), 6.46-6.75 (m, 4H), 7.06 (m, 1H), 7.13-7.35 (m, 4H)

MS (electrospray):  $m/z$  [ $\text{MH}^+$ ] 321.1;  $\text{C}_{22}\text{H}_{28}\text{N}_2 + \text{H}$  requires 321.2

#### 30 Preparation 19

##### 6-Ethyl-3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 3-(chloromethyl)-2-ethyl-2-(3-nitrophenyl)cyclopropane carboxylate (Preparation 16, 4.0 g, 12.8 mmol), was added sodium hydrogen carbonate (1.3 g, 15.4 mmol) and hexylamine (15.3 g, 20 ml, 151 mmol). The mixture was heated to 150°C for 12 h, then cooled to room temperature and partitioned between hydrochloric acid (2N, 500 ml) and ethyl acetate (2 x 500 ml). The combined organic layers were washed with water (500 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (200 g) column chromatography eluting with a gradient of dichloromethane/ethyl acetate 100:0 to 90:10. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as an orange oil (1.4 g, 32%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.93 (m, 6H), 1.30 (m, 6H), 1.52 (m, 2H), 1.62 (m, 2H), 2.17 (m, 1H), 2.38 (d, 1H), 3.25 (m, 2H), 3.38 (d, 1H), 3.69 (dd, 1H), 7.50 (t, 1H), 7.68 (d, 1H), 8.10 (d, 1H), 8.18 (s, 1H)

MS (electrospray): m/z [MH<sup>+</sup>] 331.1; C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> + H requires 331.2

#### Preparation 20

##### 3-(6-Ethyl-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine

To a solution of 6-ethyl-3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 19, 1.4 g, 4.2 mmol) in anhydrous tetrahydrofuran (42 ml) at room temperature under nitrogen, was added dropwise a solution of lithium aluminium hydride (1.0 M in tetrahydrofuran, 23 ml, 23 mmol), then the mixture was gently heated under reflux for 18 h. The mixture was cooled, then quenched by carefully pouring onto ice cold hydrochloric acid (1N, 400 ml). The acidic layer was extracted with diethyl ether (2 x 200 ml). The pH of the aqueous layer was adjusted to 10 by the addition of potassium carbonate and then was extracted with diethyl ether (300 ml). The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a yellow oil (1.2 g). This was dissolved in ethanol (50 ml), Raney nickel (100 mg) was added, then the mixture was placed under an atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 60°C for 40 h. The mixture was cooled, filtered through Arbocel™, and concentrated *in vacuo* to give the title compound as a very pale yellow oil (1.1 g, 77%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (m, 6H), 1.27 (m, 6H), 1.44 (m, 2H), 1.87 (m, 4H), 2.48 (m, 2H), 2.93 (m, 4H), 6.46-6.73 (m, 3H), 7.04 (m, 1H)

MS (electrospray):  $m/z$  [MH<sup>+</sup>] 287.1; C<sub>19</sub>H<sub>30</sub>N<sub>2</sub> + H requires 287.2

5 Preparation 21

(E)-3-(3-Nitrophenyl)-2-propen-1-ol

To a solution of ethyl (E)-3-(3-nitrophenyl)-2-propenoate (8.04 g, 36 mmol) in dichloromethane at 0°C under nitrogen was added dropwise over 5 minutes diisobutylaluminium hydride (1.0 M solution in dichloromethane, 80 ml, 80 mmol). The mixture was stirred at 0 °C for 10 minutes, then allowed to warm to room temperature over 30 minutes. Hydrochloric acid (1N, 500 ml) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 x 250 ml). The organic layers were combined, washed with brine (2 x 100 ml), filtered and concentrated *in vacuo* to give the title compound as a red oil.

NMR (CDCl<sub>3</sub>)  $\delta$ : 4.40 (d, 2H), 6.50 (dt, 1H), 6.70 (d, 1H), 7.48 (t, 1H), 7.67 (d, 1H), 8.09 (d, 1H), 8.23 (s, 1H).

Preparation 22

20 1-[(E)-3-Bromo-1-propenyl]-3-nitrobenzene

To a solution of triphenylphosphine (1.47 g, 5.6 mmol) in acetonitrile (35 ml) at 0°C was added dropwise over 5 minutes a solution of bromine (0.88g, 5.6 mmol) in acetonitrile (5 ml) at a rate such that the temperature was kept between 5°C and 10°C. The mixture was then allowed to warm to room temperature, then to this was added dropwise a solution of (E)-3-(3-nitrophenyl)-2-propen-1-ol (Preparation 21, 1 g, 5.6 mmol) in acetonitrile (5 ml). The mixture was warmed to 65 °C for 40 min, cooled to room temperature, and poured onto diethyl ether (150 ml). The mixture was concentrated *in vacuo*. The residue was purified by silica (10 g) column chromatography eluting with hexane then dichloromethane. Product-containing fractions were combined and concentrated *in vacuo*, and the residue recrystallised from cyclohexane to give the title compound as a very pale yellow solid (0.82g, 61%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 4.18 (d, 2H), 6.48-6.60 (m, 1H), 6.72 (d, 1H), 7.52 (t, 1H), 7.68 (d, 1H), 8.12 (d, 1H), 8.24 (s, 1H).

### Preparation 23

#### 5 Ethyl 2-(bromomethyl)-3-(3-nitrophenyl)cyclopropane carboxylate

To a solution of 1-[(E)-3-bromo-1-propenyl]-3-nitrobenzene (Preparation 22, 820 mg, 3.23 mmol) in dichloromethane (3 ml) was added rhodium (II) acetate dimer (20 mg, 0.046 mmol). To the mixture was added dropwise at room temperature over 3 h a  
10 solution of ethyl diazoacetate (0.47 ml, 510 mg, 4.47 mmol) in dichloromethane (3 ml), then the mixture was stirred at room temperature for 66 h. The mixture was purified by silica (100 g) column chromatography eluting with hexane:dichloromethane 100:0 to 50:50. Product containing fractions were combined and concentrated *in vacuo* to afford the title compound as a colourless oil (65 mg, 7%).

15 NMR (CDCl<sub>3</sub>)  $\delta$ : 1.33 (t, 3H), 2.20 (m, 1H), 2.35 (m, 1H), 2.80 (m, 1H), 3.74 (t, 1H), 3.90 (m, 1H), 4.25 (m, 2H), 7.58 (m, 2H), 7.98 (s, 1H), 8.09 (m, 1H)

### Preparation 24

#### 6-(3-Nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one

20

To a solution of ethyl 2-(bromomethyl)-3-(3-nitrophenyl)cyclopropane carboxylate (Preparation 23, 60 mg, 0.18 mmol) in N,N-dimethylformamide (2 ml) was added sodium hydrogen carbonate (30 mg, 0.36 mmol) and 3-phenylpropylamine (30 mg, 31  $\mu$ l, 0.22 mmol). The mixture was heated to 150 °C for 1 hour, then cooled to room  
25 temperature and stirred for 16 hours. Water (30 ml) was added and the mixture was extracted with diethyl ether (2 x 50 ml). The combined extracts were concentrated *in vacuo* and the residue was purified by silica (5 g) column chromatography eluting with dichloromethane then 4:1 dichloromethane:ethyl acetate. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless  
30 glassy solid (55 mg, 90%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.85 (m, 2H), 2.02 (m, 1H), 2.20 (m, 1H), 2.32 (m, 1H), 2.64 (t, 2H), 3.20-3.40 (m, 2H), 3.49 (d, 1H), 3.65 (dd, 1H), 7.14-7.49 (m, 7H), 7.87 (s, 1H), 8.05 (d, 1H)

MS (APCI): m/z [MH<sup>+</sup>] 337.2; C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> + H requires 337.2

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#### Preparation 25

##### 3-[3-(3-Phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl amine

To a solution of 6-(3-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one  
10 (Preparation 24, 55 mg, 0.16 mmol) in tetrahydrofuran (3 ml) under nitrogen, was added dropwise at room temperature a 1.0 M solution of lithium aluminium hydride in tetrahydrofuran (0.81 ml, 0.81 mmol). The mixture was heated to 60°C for 4 h. Further lithium aluminium hydride in tetrahydrofuran (1.0M, 0.3 ml, 0.3 mmol) was added, and the mixture was heated at 60 °C for 20 minutes, then cooled to room temperature. Water  
15 (30 ml) was carefully added, then the residue was acidified by the addition of 2N hydrochloric acid (5 ml), and then basified with 2N sodium hydroxide solution (6 ml). The mixture was extracted with ethyl acetate (3 x 50ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was dissolved in ethanol (5 ml), Raney nickel (50 mg) was added, and the mixture was placed under an  
20 atmosphere of hydrogen (2 atm, 203 kPa) and stirred at 60°C for 16 h. The mixture was filtered through Celite™ and concentrated *in vacuo* to give the title compound as a pale yellow oil (35 mg, 75%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.74 (m, 2H), 1.95 (m, 2H), 2.39 (br.s, 1H), 2.65 (m, 6H), 3.38 (br.d, 2H), 6.28-6.50 (m, 3H), 7.05 (m, 1H), 7.15-7.34 (m, 5H).

25 MS (thermospray) : M/Z [MH<sup>+</sup>] 293.3; C<sub>20</sub>H<sub>24</sub>N<sub>2</sub> + H requires 293.2

#### Preparation 26

##### Ethyl 2-(bromomethyl)-3-phenylcyclopropanecarboxylate

30 To a solution of [(E)-3-bromo-1-propenyl]benzene (705 mg, 3.58 mmol) in dichloromethane (1 ml) was added rhodium (II) acetate dimer (20 mg, 0.05 mmol). To the mixture was added dropwise at room temperature over 4 h a solution of ethyl

diazoacetate (0.43 ml, 0.47 g, 4.15 mmol) in dichloromethane (2.5 ml). The mixture was stirred at room temperature for 60 h. The mixture was purified by silica column (40 g) chromatography eluting with 1:1 hexane:dichloromethane then dichloromethane. Product-containing fractions were purified further by silica column (10 g) chromatography eluting with 9:1 hexane:dichloromethane then dichloromethane. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil (75 mg, 8%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.32 (t, 3H), 2.16 (m, 1H), 2.27 (dd, 1H), 2.70 (t, 1H), 3.76 (t, 1H), 3.90 (dd, 1H), 4.23 (m, 2H), 7.12 (d, 2H), 7.17-7.36 (m, 3H)

#### Preparation 27

##### 3-Hexyl-6-phenyl-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 2-(bromomethyl)-3-phenylcyclopropanecarboxylate (Preparation 26, 65 mg, 0.22 mmol) in N,N-dimethylformamide (2 ml) was added sodium hydrogen carbonate (30 mg, 0.36 mmol) and hexylamine (33  $\mu$ l, 26 mg, 0.26 mmol), and the mixture was heated to 150°C for 3 h. The mixture was cooled, water (30ml) was added, and the mixture was extracted with diethyl ether (2 x 30 ml). The extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The mixture was purified by silica column (5 g) chromatography eluting with 4:1 dichloromethane:ethyl acetate. Product-containing fractions were combined and concentrated *in vacuo* to give the title compound as a colourless oil (45 mg, 76%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.89 (t, 3H), 1.28 (m, 6H), 1.48 (m, 2H), 2.00 (m, 1H), 2.12 (m, 1H), 2.22 (m, 1H), 3.08-3.31 (m, 2H), 3.47 (d, 1H), 3.63 (m, 1H), 7.03 (d, 2H), 7.12-7.33 (m, 3H)

MS (APCI) : M/Z [MH<sup>+</sup>] 258.1; C<sub>17</sub>H<sub>23</sub>NO + H requires 258.2

#### Preparation 28

##### 3-Benzyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one

A solution of ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)cyclopropane carboxylate (Preparation 5, 10 g, 33.6 mmol) in benzylamine (21.6 g, 201.6 mmol) was heated to

160°C for 16 h. The mixture was cooled, 2N hydrochloric acid was added (200 ml), and the mixture was extracted with dichloromethane (3 x 250 ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica (600 g) column chromatography eluting with dichloromethane, then a gradient of  
5 dichloromethane:ethyl acetate ending with pure ethyl acetate. Appropriate fractions were combined and concentrated *in vacuo* to give the title compound as an amber oil (6 g, 55 %).

NMR (CDCl<sub>3</sub>) δ: 1.27 (s, 3H), 2.13 (t, 1H), 2.42 (d, 1H), 3.25 (d, 1H), 3.62 (dd, 1H), 4.31 (d, 1H), 4.57 (d, 1H), 7.33 (m, 5H), 7.49 (t, 1H), 7.63 (d, 1H), 8.08 (d, 1H),  
10 8.13 (s, 1H)

MS (electrospray) : M/Z [MH<sup>+</sup>] 323.1; C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> + H requires 323.1

#### Preparation 29

##### 6-(3-Aminophenyl)-3-benzyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one

15 To a solution of 3-benzyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 28, 2 g, 6.2 mmol) in absolute ethanol (170 ml) was added water (30 ml), calcium chloride (344 mg, 3.1 mmol) and iron powder (3.02 g, 53.8 mmol). The mixture was heated to reflux under nitrogen for 4 h, then cooled. The solution was  
20 filtered through silica (10 g) eluting with methanol, then concentrated *in vacuo* to give the title compound as a white solid (1.73 g, 95%).

mp 150-151°C

NMR (CDCl<sub>3</sub>) δ: 1.22 (s, 3H), 2.03 (t, 1H), 2.33 (d, 1H), 3.15 (d, 1H), 3.53 (dd, 1H), 4.23 (d, 1H), 4.54 (d, 1H), 6.53 (d, 1H), 6.66 (m, 2H), 7.05 (t, 1H), 7.30 (m, 5H)

25 MS (electrospray) : M/Z [MH<sup>+</sup>] 293.1; C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O + H requires 293.2

#### Preparation 30

##### 3-(3-Benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine

30 Lithium aluminium hydride (1M in tetrahydrofuran, 11.84 ml, 11.84 mmol) was added dropwise to dry tetrahydrofuran (60 ml) under nitrogen. 6-(3-Aminophenyl)-3-benzyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 29, 1.73 g, 5.90 mmol) was



suspended in dry tetrahydrofuran (100 ml) and added slowly to the lithium aluminium hydride solution by cannula. The reaction was then heated at 50°C for 2 hours. After cooling, water (20 ml) was cautiously added to the solution, the pH of the aqueous layer was adjusted to 4 by the addition of 2N hydrochloric acid and then adjusted to 10 using dilute sodium hydroxide solution. The mixture was extracted with ethyl acetate (3 x 200 ml), and the combined extracts were washed with water (100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the title compound as a yellow oil (1.58 g, 96 %).

NMR (CDCl<sub>3</sub>) δ: 1.60 (s, 3H) , 1.78 (s, 2H), 2.83 (d, 2H), 3.02 (d, 2H), 3.67 (s, 2H), 6.48 (d, 1H), 6.60 (s, 1H), 6.67 (d, 1H), 7.05 (t, 1H), 7.33 (m, 5H).

MS (electrospray) : M/Z [MH<sup>+</sup>] 279.1; C<sub>19</sub>H<sub>22</sub>N<sub>2</sub> + H requires 279.2

### Preparation 31

#### Ethyl (E)-3-(3-cyanophenyl)-2-butenolate

To a solution of sodium hydride 60% dispersion in oil (8.28g, 0.19 mol) in tetrahydrofuran (300 ml) stirred at 0°C under nitrogen was added dropwise over 45 minutes triethyl phosphonoacetate (46.2 g, 0.21 mol). The mixture was then stirred at room temperature for 30 minutes. 3-Cyanoacetophenone (25.1 g, 0.172 mol) in tetrahydrofuran (200 ml) was added *via* a cannula at room temperature and the brown reaction mixture was stirred for 1 h. Saturated ammonium chloride solution (150 ml) was added, and the mixture was concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 150 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography eluting with a gradient of hexane:ethyl acetate 100:0 to 70:30 to afford the title compound as a mixture of the *E* and *Z* isomers (ratio 5:1) as a colourless oil which solidified on standing. This was taken on without further purification.

NMR (CDCl<sub>3</sub>) for the *E* isomer δ: 1.34 (t, 3H), 2.58 (s, 3H), 4.25 (q, 2H), 6.15 (s, 1H), 7.50 (t, 1H), 7.62-7.70 (m, 2H), 7.77 (s, 1H)

### Preparation 32

#### (E)-3-(3-Cyanophenyl)-2-butenic acid

To a mixture of lithium hydroxide monohydrate (10.8 g, 0.26 mol) in tetrahydrofuran (100 ml) and water (100 ml) was added crude ethyl (*E*)-3-(3-cyanophenyl)-2-butenate (Preparation 31) in tetrahydrofuran (150 ml). The resultant mixture was made homogeneous by the addition of methanol (approx. 50 ml), and then stirred at room temperature for 16 h. The mixture was concentrated *in vacuo* and acidified with 2N hydrochloric acid, following which a solid precipitated. The solid was collected by suction filtration, washing with cold water. The solid was then dried and recrystallised from acetonitrile.

From the first crop, 15.8 g (49% over 2 steps) of the pure *E*-isomer was isolated.

NMR (CDCl<sub>3</sub>)  $\delta$ : 2.58 (s, 3H), 6.18 (s, 1H), 7.58 (t, 1H), 7.72 (d, 1H), 7.81 (d, 1H), 7.90 (s, 1H)

### Preparation 33

#### 3-[(*E*)-3-Hydroxy-1-methyl-1-propenyl]benzonitrile

To a solution of (*E*)-3-(3-cyanophenyl)-2-butenic acid (Preparation 32, 15.83 g, 84.6 mmol) and triethylamine (8.99 g, 88.8mmol) in tetrahydrofuran (150 ml) at 0°C was added over 10 minutes ethyl chloroformate (9.65 g, 88.8 mmol). The mixture was then stirred at 0°C for 30 minutes and at room temperature for a further 30 minutes. The resulting precipitate was collected by filtration and the solid was washed with cold tetrahydrofuran (2 x 30 ml). The preformed mixed anhydride in tetrahydrofuran was then added over 30 minutes *via* cannula to sodium borohydride (11.2 g, 0.30 mol) in a mixture of tetrahydrofuran/water (4:1, 100ml) at 0°C. The resultant mixture was stirred at 0°C for 1 h, at room temperature for 3 h and then cooled to 0°C. 2N Hydrochloric acid was added cautiously until effervescence had ceased. The mixture was concentrated *in vacuo* and 1N hydrochloric acid (100 ml) was added. The aqueous solution was extracted with ethyl acetate (3 x 150 ml) and the combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude oil was purified by silica column chromatography eluting with a gradient of ethyl acetate:hexane (1:1 to 100:0). An impurity, unreacted starting carboxylic acid, was removed by a basic wash with 2N sodium hydroxide solution (150ml) and the pure product was extracted with

dichloromethane (3 x 100 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (11.9 g, 82%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.4 (t, 1H), 2.05 (br. s, 3H), 4.40 (t, 2H), 6.01 (m, 1H), 7.42 (t, 1H), 7.57 (d, 1H), 7.62 (d, 1H), 7.68 (s, 1H)

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#### Preparation 34

##### 3-[(E)-3-Chloro-1-methyl-1-propenyl]benzonitrile

To a solution of N-chlorosuccinimide (9.8 g, 73.1 mmol) in dichloromethane (25 ml) at -10°C was added dropwise over 15 minutes dimethylsulfide (5.4 ml, 73.1 mmol). The mixture was stirred at -10°C for 30 min, then a solution of 3-[(E)-3-hydroxy-1-methyl-1-propenyl]benzonitrile (from Preparation 33, 11.9 g, 69.6 mmol) in dichloromethane (20 ml) was added dropwise over 15 minutes at -10°C. The mixture was stirred at 0°C for 1 h, and was then poured onto saturated brine (50 ml). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The extracts were combined, washed with water (50 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude pale yellow oil (13.1 g, 100%) was used directly in the next step.

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NMR (CDCl<sub>3</sub>)  $\delta$ : 2.16 (s, 3H), 4.27 (d, 2H) 6.04 (t, 1H), 7.42 (t, 1H), 7.59 (d, 1H), 7.63 (d, 1H), 7.68 (s, 1H)

20

#### Preparation 35

##### Ethyl 3-(chloromethyl)-2-(3-cyanophenyl)-2-methylcyclopropane carboxylate

To a solution of 3-[(E)-3-chloro-1-methyl-1-propenyl]benzonitrile (Preparation 34, 13.1 g, 69.6 mmol) in dichloromethane (20 ml) was added rhodium (II) acetate dimer (0.46 g, 1.0 mmol). To the mixture was added dropwise at room temperature over 8 h (*via* a syringe pump) a solution of ethyl diazoacetate (14.6 ml, 0.14 mol) in dichloromethane (20 ml). The solvent was removed *in vacuo* and the crude residue was then partially purified by silica column chromatography eluting with dichloromethane:hexane (80:20). This material was then dissolved in dichloromethane (20 ml) containing rhodium (II) acetate dimer (0.46 g, 1.0 mmol). To this mixture was added dropwise a solution of

30

ethyl diazoacetate (14.6 ml, 0.14 mol) in dichloromethane (20 ml) at room temperature over 8 h. The mixture was concentrated *in vacuo* and the residue purified by silica column chromatography eluting with hexane:dichloromethane (80:20) and then hexane:diethyl ether (80:20) to give the title compound as a colourless oil which solidified on standing (5.82 g, 30%).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.30 (t, 3H), 1.58 (s, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 4.00 (dd, 1H), 4.17 - 4.27 (m, 3H), 7.43 (t, 1H), 7.56 (d, 1H), 7.58 (d, 1H), 7.62 (s, 1H)

#### Preparation 36

##### 10 3-(3-Hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzonitrile

To a solution of ethyl 3-(chloromethyl)-2-(3-cyanophenyl)-2-methylcyclopropanecarboxylate (Preparation 35, 5.82 g, 21.1 mmol) in *N,N*-dimethylformamide (20 ml) at room temperature was added sodium hydrogen carbonate (1.77 g, 21.1 mmol) followed by hexylamine (16.7 ml, 0.13 mol). The mixture was then heated under reflux for 16 h, cooled to room temperature and poured onto ice. After warming to room temperature, the mixture was partitioned against diethyl ether (50 ml). The two layers were separated and the aqueous layer was extracted with diethyl ether (2 x 30 ml). The ethereal extracts were washed with water (50 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude oil was purified by silica column chromatography eluting with a gradient of hexane:ethyl acetate (5:1 to 0:100) to afford the title compound (2.2 g, 35%) as a colourless oil.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.91 (m, 3H), 1.20-1.40 (m, 9H), 1.47-1.58 (m, 2H), 2.10 (m, 1H), 2.30 (m, 1H), 3.10-3.38 (m, 3H), 3.70 (dd, 1H), 7.41 (t, 1H), 7.56 (m, 2H), 7.59 (s, 1H).

#### Preparation 37

##### 30 3-[6-Methyl-2-oxo-3-(3-phenylpropyl)-3-azabicyclo [3.1.0]hex-6-yl]-benzonitrile

To a solution of ethyl 3-(chloromethyl)-2-(3-cyanophenyl)-2-methylcyclopropanecarboxylate (Preparation 35, 170 mg, 0.62 mmol) in *N,N*-dimethylformamide (6.0 ml) at

room temperature was added sodium hydrogen carbonate (52 mg, 0.62 mmol) followed by 3-phenylpropylamine (0.35 ml, 2.47 mmol). The mixture was heated at 100°C for 6 h and under reflux for 5 h. After the mixture had cooled to room temperature, water (4 ml) was added and the aqueous layer was extracted with diethyl ether (3 x 4 ml). The combined ethereal extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude oil was purified by silica column chromatography eluting with a gradient of hexane:ethyl acetate (50:50 to 0:100) to afford the title compound (80 mg, 40%) as a colourless oil.

NMR (CDCl<sub>3</sub>) δ: 1.35 (s, 3H), 1.87 (m, 2H), 2.10 (t, 1H), 2.30 (d, 1H), 2.64 (m, 2H), 3.16-3.40 (m, 3H), 3.70 (dd, 1H), 7.17-7.60 (m, 9H)

#### Preparation 38

6-Methyl-3-(3-phenylpropyl)-6-{3-[5-(trimethylsilyl)-1H-1,2,3-triazol-5-yl]phenyl}-3-azabicyclo[3.1.0]hexan-2-one

To a solution of (trimethylsilyl)diazomethane (0.36 ml, 0.74 mmol) in tetrahydrofuran (4 ml) at 0°C was added *n*-butyllithium (0.40 ml, 0.64 mmol) dropwise over a few minutes. The mixture was then stirred at 0°C for 30 minutes. To this mixture was added 3-[6-methyl-2-oxo-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hex-6-yl]benzonitrile (Preparation 37, 78.0 mg, 0.24 mmol) in tetrahydrofuran (2 ml) at 0°C *via* a cannula. The mixture was then allowed to warm to room temperature and stirred for 16 h. Further reaction was quenched by the addition of saturated ammonium chloride solution (5 ml) and the aqueous layer was extracted with ethyl acetate (3 x 5 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude oil was purified by silica column chromatography eluting with a gradient of hexane:ethyl acetate (50:50 to 0:100) to afford the title compound (58 mg, 55%) as a colourless oil.

NMR (CDCl<sub>3</sub>) δ: 0.37 (s, 9H), 1.38 (s, 3H), 1.85 (m, 2H), 2.09 (t, 1H), 2.40 (d, 1H), 2.64 (m, 2H), 3.16-3.44 (m, 3H), 3.65 (dd, 1H), 7.17-7.45 (m, 8H), 7.64 (s, 1H)

#### Preparation 39

3-Hexyl-6-methyl-6-{3-[5-(trimethylsilyl)-1H-1,2,3-triazol-5-yl]phenyl}-3-azabicyclo[3.1.0]hexan-2-one

To a solution of (trimethylsilyl)diazomethane (4.32 ml, 8.64 mmol) in tetrahydrofuran (10 ml) at 0°C was added *n*-butyllithium (3.46 ml, 8.64 mmol) dropwise over 10 minutes. The mixture was then stirred at 0°C for 30 minutes. To this mixture was  
5 added 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzonitrile (Preparation 36, 852 mg, 2.88 mmol) in tetrahydrofuran (12 ml) at 0°C *via* cannula. The mixture was then allowed to warm to room temperature and stirred for 48 h. Further reaction was quenched by the addition of saturated ammonium chloride solution (25 ml), and the tetrahydrofuran was removed *in vacuo*. The aqueous solution was extracted with ethyl  
10 acetate (3 x 20 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude oil was purified by silica column chromatography, eluting with a gradient of hexane:ethyl acetate (66:33 to 0:100) to afford the title compound (1.2 g, 100%) as a colourless oil.

NMR (CDCl<sub>3</sub>) δ: 0.38 (s, 9H), 0.82-0.95 (m, 3H), 1.30-1.40 (m, 9H), 1.47-1.58 (m,  
15 2H), 2.08 (t, 1H), 2.40 (d, 1H), 3.10-3.38 (m, 3H), 3.67 (dd, 1H), 7.30-7.45 (m, 3H), 7.63 (s, 1H).

#### Preparation 40

##### 3-Hexyl-6-methyl-6-[3-(1*H*-1,2,3-triazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one

To a solution of 3-hexyl-6-methyl-6-{3-[5-(trimethylsilyl)-1*H*-1,2,3-triazol-4-yl]phenyl}-3-azabicyclo[3.1.0]hexan-2-one (Preparation 39, 1.2 g, 2.88 mmol) in ethanol (15 ml) was added potassium fluoride (183 mg, 3.17 mmol) and a few drops of concentrated hydrochloric acid. The mixture was heated at reflux for 1.5 hours and then cooled to  
25 room temperature. The solvent was removed *in vacuo* and the crude residue was dissolved in dichloromethane (40 ml) and washed with 10% potassium carbonate solution. The extract was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give the crude product which was used directly in the next step.

NMR (CDCl<sub>3</sub>) δ: 0.80-0.98 (m, 3H), 1.25-1.40 (m, 9H), 1.43-1.58 (m, 2H), 2.10 (t,  
30 1H), 2.43 (d, 1H), 3.13-3.40 (m, 3H), 3.65-3.76 (m, 1H), 7.25-7.38 (m, 2H), 7.63 (d, 1H), 7.86 (s, 1H), 7.99 (s, 1H)

Preparation 416-Methyl-3-(3-phenylpropyl)-6-[3-(1*H*-1,2,3-triazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one

- 5 To a solution of 6-methyl-3-(3-phenylpropyl)-6-{3-[5-(trimethylsilyl)-1*H*-1,2,3-triazol-4-yl]phenyl}-3-azabicyclo[3.1.0]hexan-2-one (Preparation 38, 58.0 mg, 0.13 mmol) in ethanol (2 ml) was added potassium fluoride (8.3 mg, 0.14 mmol) and a drop of concentrated sulphuric acid. The mixture was heated at reflux for 4 hours and then stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the  
10 crude residue was absorbed onto silica. This material was then purified by silica column chromatography eluting first with hexane:ethyl acetate (1:1) and then increasing gradually to neat ethyl acetate. The desired title compound (32 mg, 66%) was isolated as a colourless oil.

- NMR (CDCl<sub>3</sub>)  $\delta$ : 1.38 (s, 3H), 1.85 (p, 2H), 2.09 (t, 1H), 2.45 (d, 1H), 2.65 (m, 2H),  
15 3.19-3.48 (m, 3H), 3.70 (dd, 1H), 7.17-7.40 (m, 7H), 7.66 (d, 1H), 7.86 (br. s, 1H), 7.99 (s, 1H)

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 373.5; C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O + H requires 373.2

Preparation 42

- 20 Ethyl 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzene carboximidoate

- Hydrogen chloride gas was bubbled through a solution of 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzonitrile (Preparation 36, 0.55 g, 1.86 mmol) in ethanol (8  
25 ml) at 0°C for 1 h. The reaction vessel was then sealed and left standing in the fridge for 48 h. The mixture was allowed to warm to room temperature and the solvent was removed *in vacuo* (to afford the title compound as its hydrochloride salt). The residue was dissolved in dichloromethane (20 ml) and washed with 10% w/v potassium carbonate solution (2 x 10 ml). The organic layer was dried (MgSO<sub>4</sub>), filtered and  
30 concentrated *in vacuo*. The crude title compound (700 mg) was isolated as a colourless oil which was taken on without further purification.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.91 (m, 3H), 1.20-1.38 (m, 9H), 1.42 (t, 3H), 1.44-1.58 (m, 2H), 2.10 (m, 1H), 2.35 (m, 1H), 3.10-3.38 (m, 3H), 3.68 (dd, 1H), 4.38 (t, 2H), 7.30-7.44 (m, 2H), 7.60 (m, 1H), 7.68 (s, 1H).

## 5 Preparation 43

### 3-Hexyl-6-methyl-6-[3-(4H-1,2,4-triazol-3-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one

To a solution of crude ethyl 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzenecarboximidoate (Preparation 42, 700 mg, 1.86 mmol) in methanol (5 ml) was added formic acid hydrazide (123 mg, 2.05 mmol) and the mixture was heated under reflux for 90 min. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was heated to 150°C for 12 h. The mixture was cooled and purified directly by silica column chromatography eluting with ethyl acetate:methanol (95:5) to afford the title compound (400 mg, 64%) as a colourless gum.

15 NMR (CDCl<sub>3</sub>)  $\delta$ : 0.83-0.94 (m, 3H), 1.22-1.38 (m, 9H), 1.44-1.58 (m, 2H), 2.17 (t, 1H), 2.41 (m, 1H), 3.10-3.38 (m, 3H), 3.68 (dd, 1H), 7.36-7.43 (m, 2H), 7.92-7.99 (m, 2H), 8.20 (s, 1H)

## Preparation 44

### 20 3-Hexyl-6-[3-(1H-imidazol-2-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]hexan-2-one

To a solution of ethyl 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzenecarboximidoate hydrochloride (Preparation 42, 528 mg, 1.45 mmol) in methanol (6 ml) at room temperature was added aminoacetaldehyde dimethylacetal (0.16 g, 1.52 mmol). The mixture was heated under reflux for 90 min, cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was dissolved in 6N hydrochloric acid (8 ml) and the mixture was heated to 80°C for 30 min and then left at room temperature for 2 h. The mixture was diluted with water (5 ml), the pH was adjusted to 9 using 5N sodium hydroxide solution and the aqueous solution was extracted with ethyl acetate (3 x 20ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography



eluting with ethyl acetate:methanol:ammonia solution (0.880) (90:10:1) to afford the title compound (190 mg, 39%) as a colourless oil.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.91 (m, 3H), 1.18 (s, 3H), 1.24-1.38 (m, 6H), 1.44-1.58 (m, 2H), 2.0 (m, 1H), 2.18 (m, 1H), 3.08-3.38 (m, 3H), 3.62 (dd, 1H), 7.12-7.35 (m, 4H),  
5 7.58 (s, 1H), 7.82 (d, 1H).

#### Preparation 45

##### N-[3-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]acetamide

10 To a solution of 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 1.30 g, 4.8 mmol) and triethylamine (3.34 ml, 24.0 mmol) in dichloromethane (30 ml) at room temperature was slowly added acetyl chloride (0.48 ml, 6.72 mmol). The mixture was stirred at room temperature overnight and then saturated ammonium chloride solution (50 ml) was added. The two layers were separated and the  
15 aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography eluting with ethyl acetate:methanol:ammonia solution (0.880) (90:10:1) to afford the title compound (1.5 g, 100%) as a colourless gum.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.95 (m, 3H), 1.25-1.38 (m, 6H), 1.38-1.43 (m, 2H), 1.50 (s, 3H), 1.76 (m, 2H), 2.18 (s, 3H), 2.42 (m, 2H), 2.78 (m, 2H), 2.98 (m, 2H), 7.00 (d, 2H), 7.10-7.30 (m, 3H), 7.38 (s, 1H).  
20

#### Preparation 46

##### N-[5-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-2-nitrophenyl]-acetamide

25

To a solution of N-[3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]acetamide (Preparation 45, 1.5 g, 4.78 mmol) in acetonitrile (20 ml) at 0°C was added nitronium tetrafluoroborate (1.0 g, 7.53 mmol) in several portions over 5 minutes. The mixture was stirred at 0 °C for 30 minutes and then saturated sodium hydrogen carbonate  
30 solution (30 ml) was added. The aqueous mixture was extracted with ethyl acetate (3 x 15 ml) and the combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography eluting with

ethyl acetate:hexane (50:50) to afford the title compound (534 mg, 32%) as pale yellow platelets.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.92 (m, 3H), 1.25-1.45 (m, 8H), 1.58 (s, 3H), 1.80 (m, 2H), 2.28 (s, 3H), 2.40 (t, 2H), 2.78 (m, 2H), 3.02 (m, 2H), 7.00 (d, 1H), 8.09 (d, 1H), 8.64 (s, 1H), 10.4 (broad s, 1H)

MS (thermospray):  $m/z$  [MH<sup>+</sup>] 360.2; C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> + H requires 360.2

#### Preparation 47

##### 5-(3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-2-nitrophenylamine

To a solution of potassium hydroxide (100 mg, 1.79 mmol) in methanol (5.0 ml) and water 2.0 ml) was added *N*-[5-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-2-nitrophenyl]acetamide (Preparation 46, 534 mg, 1.49 mmol) in methanol (5 ml). The mixture was heated under reflux for 30 minutes and then was allowed to cool. The solvent was removed *in vacuo*, water (5 ml) was added and the aqueous solution was extracted with ethyl acetate (3 x 5 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the title compound (360 mg, 76%) as a crude oil which was used without further purification.

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.82-0.95 (m, 3H), 1.25-1.45 (m, 8H), 1.56 (s, 3H), 1.79 (m, 2H), 2.42 (t, 2H), 2.80 (m, 2H), 3.00 (m, 2H), 6.00 (broad s, 2H), 6.53 (d, 1H), 6.63 (s, 1H), 7.99 (d, 1H)

#### Preparation 48

##### 2-Amino-4-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl) phenylamine

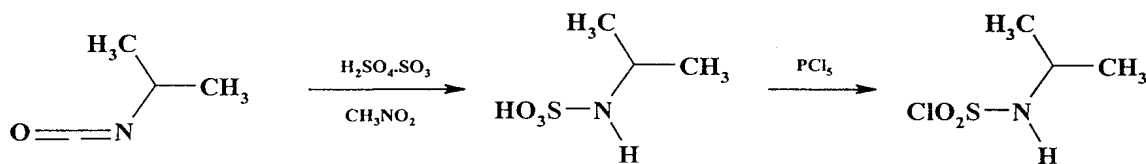
To a solution of 5-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-2-nitrophenylamine (Preparation 47, 360 mg, 1.14 mmol) in ethanol (15 ml) was added 10% palladium on carbon (50 mg). The mixture was placed under an atmosphere of hydrogen (50 psi, 345 kPa) and heated at 50°C for 16 hours. The mixture was then cooled and filtered through Celite<sup>TM</sup>, washing with ethanol. The filtrate was concentrated *in vacuo* to give the crude title compound (328 mg, 100%) as a yellow oil which was used without further purification.

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.82-0.92 (m, 3H), 1.25-1.38 (m, 6H), 1.42-1.60 (m, 5H), 1.80 (m, 2H), 2.45-2.60 (m, 2H), 2.80-3.10 (m, 4H), 3.35 (broad s, 4H), 6.57-6.62 (m, 3H)

MS (thermospray):  $m/z$  [ $\text{MH}^+$ ] 288.4;  $\text{C}_{18}\text{H}_{29}\text{N}_3 + \text{H}$  requires 288.2

## 5 Preparation 49

### 2-[(Chlorosulfonyl)amino]propane

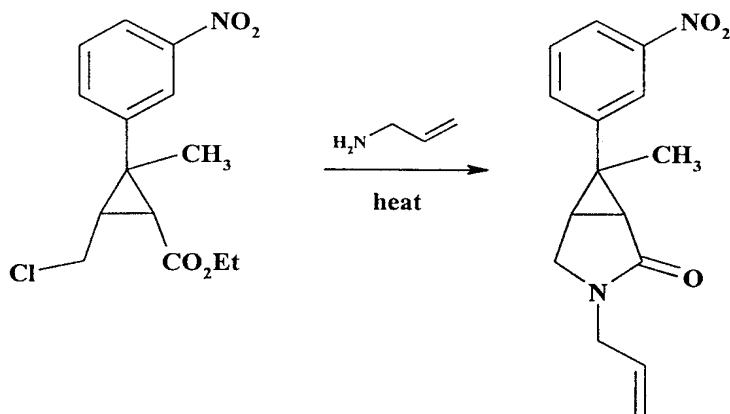


- 10 To sulfuric acid oleum (6 ml) in nitromethane (15 ml) was added dropwise over 30 min isopropyl isocyanate at 0 °C. The reaction mixture was heated under reflux for 30 min and then cooled to room temperature, the solid was collected by suction filtration and washed with diethyl ether. The solid was dissolved in toluene (6 ml) and phosphorus pentachloride (7.58 g, 36.4 mmol) was added. The reaction mixture was heated under reflux for 2.5 h
- 15 and the solvent was removed *in vacuo*. The crude product was distilled to give the title compound as an oil (b.p. 80 °C at 0.5 mmHg).

NMR ( $\text{CDCl}_3$ ): 1.35 (d, 6H), 3.9 (m, 1H), 5.4 (br, 1H).

## Preparation 50

### 20 3-Allyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one



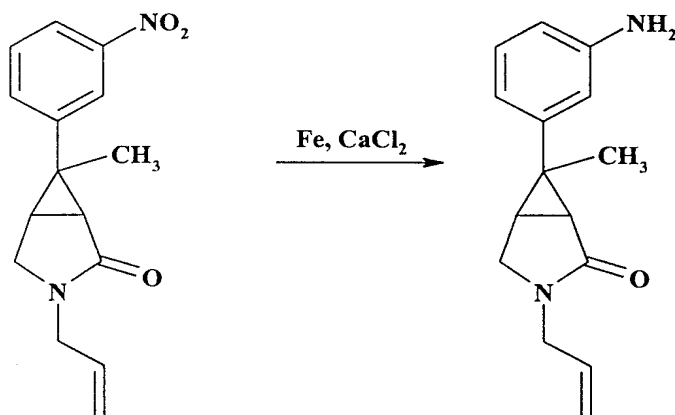
Ethyl 3-(chloromethyl)-2-methyl-2-(3-nitrophenyl)cyclopropanecarboxylate (Preparation 5, 1 g, 3.36 mmol) in allylamine (1.15 g, 20.1 mmol) was heated in a sealed tube at 150°C for 16 h. After cooling the reaction mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the crude product as a yellow oil (0.92 g, 100%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.4 (s, 3H), 2.1 (m, 1H), 2.4 (m, 1H), 3.35 (m, 1H), 3.7 (m, 1H), 3.8 - 4.0 (m, 2H), 5.2 - 5.3 (m, 2H), 5.75 (m, 1H), 7.5 (t, 1H), 7.65 (d, 1H), 8.05 (d, 1H), 8.15 (s, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 273.0; C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> + H requires 273.1.

#### Preparation 51

##### 3-Allyl-6-(3-aminophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one



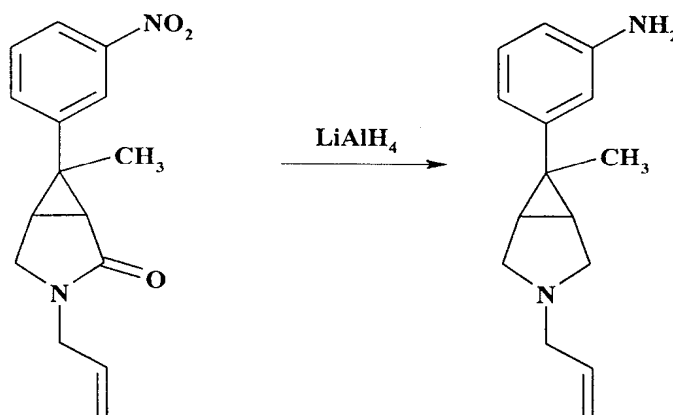
To a solution of 3-allyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 50, 10.2 g, 37.5 mmol) in ethanol (850 ml) and water (150 ml) was added iron powder (18.9 g, 337.5 mmol) and calcium chloride (2.1 g, 18.7 mmol). The reaction mixture was refluxed for 5 h, and then filtered to remove the iron powder. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in dichloromethane : methanol (85 : 15), filtered and then concentrated *in vacuo*, dissolved in tetrahydrofuran, filtered and then concentrated *in vacuo* to give the title compound as a pale yellow foam (9 g, 99%).

199

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.2 (s, 3H), 2.05 (m, 1H), 2.2 (m, 1H), 3.2 (m, 1H), 3.6 (m, 1H), 3.7 - 3.8 (m, 2H), 5.1 - 5.2 (m, 2H), 5.7 (m, 1H), 6.5 (d, 1H), 6.6 - 6.7 (m, 2H), 7.0 (t, 1H).

## 5 Preparation 52

### 3-(3-Allyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)aniline



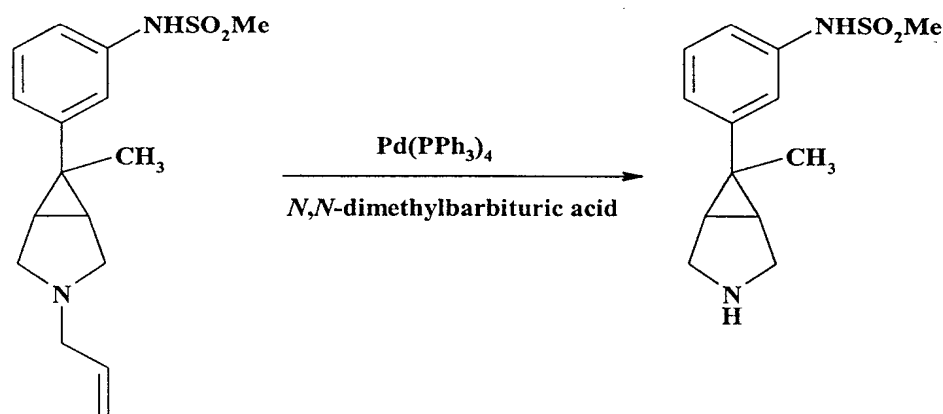
- 10 To dry tetrahydrofuran (300 ml) under nitrogen was added dropwise lithium aluminium hydride (1M in tetrahydrofuran, 75 ml, 75 mmol). To this solution, 3-allyl-6-(3-aminophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 51, 9.0 g, 37.1 mmol) dissolved in tetrahydrofuran (200 ml), was added dropwise at 0°C. The reaction mixture was stirred for 1 h and then heated to 50°C for 3 h. The reaction mixture was quenched
- 15 with water (150 ml) and solid sodium hydrogen carbonate was added. The slurry was extracted with ethyl acetate and then dichloromethane. The organic extracts were combined and dried ( $\text{Na}_2\text{SO}_4$ ) and then concentrated *in vacuo* to give the title compound as a thick yellow oil (8.5 g, 100%).

- NMR ( $\text{CDCl}_3$ , selected data for the free base) : 1.5 (s, 3H), 1.8 (m, 2H), 2.85 (m, 2H), 2.95 (m, 2H), 3.2 (m, 2H), 5.0 - 5.3 (m, 2H), 5.9 (m, 1H), 6.5 (d, 1H), 6.6 (s, 1H), 6.65 (d, 1H), 7.1 (t, 1H).
- 20

## Preparation 53

### N-[3-(6-Methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide

200

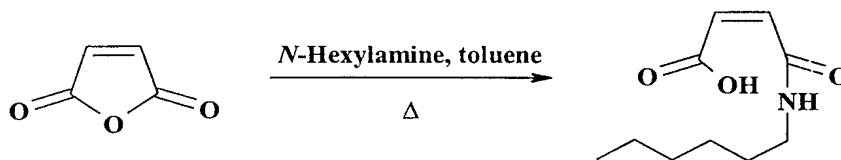


A stirred mixture of *N*-[3-(3-allyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Example 56, 1.90 g, 6.19 mmol), *tetrakis*(triphenylphosphine)palladium (0) (71.8 mg, 62.1  $\mu\text{mol}$ ) and *N,N*-dimethylbarbituric acid (2.91 g, 18.6 mmol) in dichloromethane (15 ml) was degassed and then heated to 35°C under nitrogen for 3 h. The solution was rapidly stirred with aqueous hydrochloric acid solution (2M, 40 ml) and the aqueous portion was separated, this process was repeated. The combined aqueous layers were washed with dichloromethane (7 x 50 ml), and then concentrated *in vacuo* to give the hydrochloride salt of the title compound as an off white solid (1.40 g, 74%).

NMR ( $d_6$ -DMSO, selected data for the hydrochloride salt): 1.25 (s, 3H), 2.15 (m, 2H), 2.95 (s, 3H), 3.2 (m, 2H), 3.6 (m, 2H), 6.95 - 7.05 (m, 2H), 7.1 (s, 1H), 7.2 (t, 1H), 9.6 (br, 1H). MS (ES) :  $M/Z$  ( $MH^+$ ) 267.1;  $C_{13}H_{18}N_2O_2S + H$  requires 267.1.

#### Preparation 54

#### 4-(Hexylamino)-4-oxo-2-butenic acid



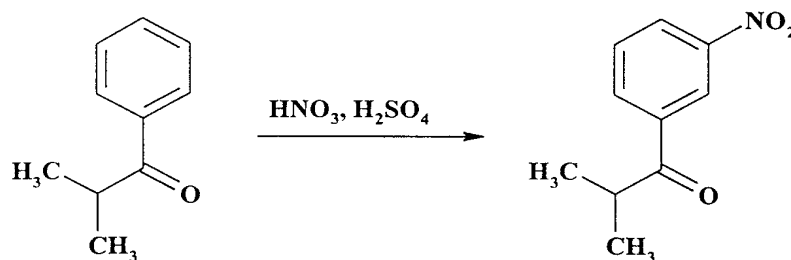
Maleic anhydride (39.4 g, 0.40 mol) was partly dissolved in toluene (1 l) to form a milky suspension. *N*-hexylamine (53 ml, 0.40 mol) was diluted with toluene (500 ml) and added

dropwise over a period of 1.5 h. After 2 h, the reaction mixture was filtered and the title compound was obtained as a white solid (76.4 g, 96%) after drying for 16 h in a vacuum oven at 40°C.

NMR (CDCl<sub>3</sub>, selected data for the free base) 0.8 (m, 3H), 1.2-1.4 (m, 6H), 1.6 (m, 2H),  
5 3.3 (m, 2H) 6.25 (d, 1H), 6.45 (d, 1H), 7.8 (br, 1H).

#### Preparation 55

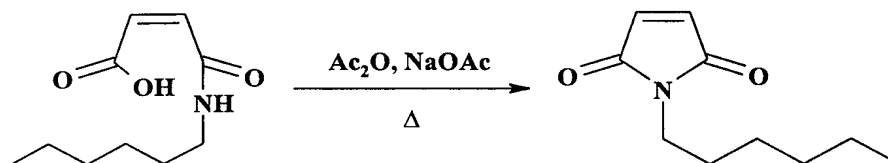
##### 2-Methyl-1-(3-nitrophenyl)-1-propanone



Concentrated nitric acid (20 ml) was added cautiously with cooling to concentrated sulphuric acid (50 ml) maintaining a temperature of -5°C. Another solution of 2-methyl-1-phenyl-1-propanone (29.6 g, 0.2 mol) in concentrated sulphuric acid (70 ml) was made up  
15 with shaking, keeping the temperature at -5°C. The former nitric acid/sulphuric acid solution was added portionwise over 30 min to the latter solution of ketone in sulphuric acid keeping the temperature at -10°C +/-5°C during the addition and for a subsequent 30 min. The reaction mixture was poured onto crushed ice (1l) and then extracted with diethyl ether (3 x 100 ml). The organic extracts were washed with water (300 ml) and then brine  
20 (300 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and then concentrated *in vacuo*. The crude product was obtained as an orange oil (40g) which was purified by chromatography on silica gel (450 g) eluting with hexane : diethyl ether (9 : 1) to give the title compound as a pale yellow solid (16.3 g, 42%), m.p.33-35°C.

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.25 (d, 6H), 3.6 (m, 1H), 7.65 (t, 1H), 8.25  
25 (d, 1H), 8.4 (d, 1H), 8.9 (s, 1H).

#### Preparation 56

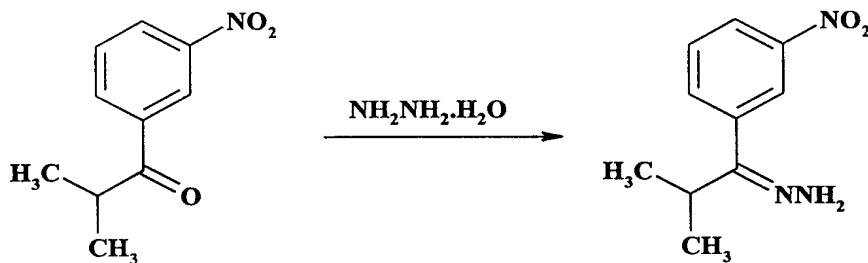
1-Hexyl -1H-pyrrole-2,5-dione

- 5 4-(Hexylamino)-4-oxo-2-butenoic acid (Preparation 54, 75.8 g, 0.38 mol) was partially dissolved in acetic anhydride (1.5 l) and sodium acetate (125.6 g, 0.19 mol) was added in one portion. The reaction mixture was gradually heated to 110°C for 4 h. Acetic anhydride was removed *in vacuo* and the title compound was obtained by vacuum distillation of the crude residue to give a colourless oil (49.8 g, 72%) which partially crystallised upon
- 10 standing.

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 6H), 1.6 (m, 2H), 3.5 (m, 2H), 6.7 (s, 2H).

Preparation 57

- 15 2-Methyl-1-(3-nitrophenyl)-1-propanone hydrazone



- To a partially dissolved solution of 2-methyl-1-(3-nitrophenyl)-1-propanone (Preparation
- 20 55, 1.0g, 5.2 mmol) in industrial methylated spirits (6 ml) was added dropwise hydrazine hydrate monohydrate (0.5 ml, 10.4 mmol). The reaction mixture was refluxed for 16 h, before cooling to room temperature and pouring into ice and water (50:50, 15 ml) giving a very fine white precipitate in a yellow solution. The mixture was extracted with diethyl ether (2 x 50 ml), the combined organic extracts were washed with brine and dried
- 25 (MgSO<sub>4</sub>), before concentrating to give an amber oil. The crude product was purified by



chromatography on silica gel eluting with dichloromethane : ethyl acetate (19:1) to give the title compound as a mixture of *cis* and *trans* hydrazones (0.54 g, 50%).

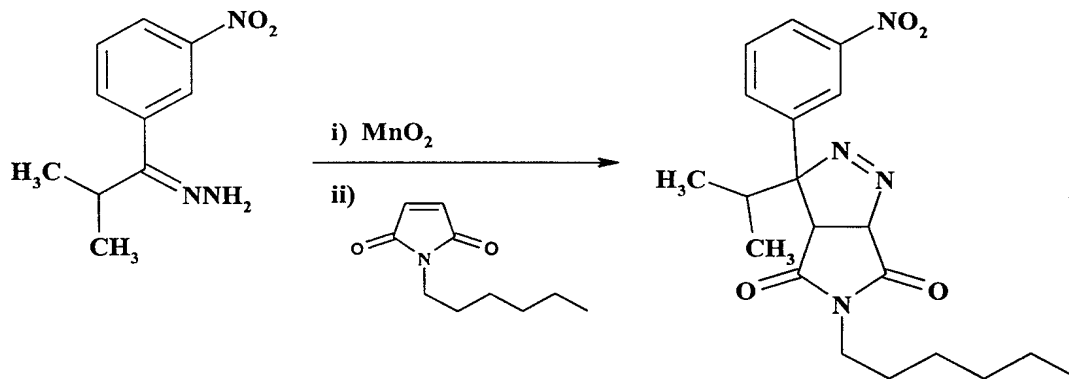
NMR (CDCl<sub>3</sub>, selected data for the free base, 2 : 1 mixture of isomers): 1.1 (d, 4H), 1.25 (d, 2H), 2.75 (m, 0.6), 3.2 (m, 0.4), 4.95 (br, 1.2), 5.6 (br, 0.8), 7.45 - 8.3 (m, 4H).

5 MS (ES) : M/Z (MH<sup>+</sup>) 208.2; C<sub>10</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> + H requires 208.1.

### Preparation 58

5-Hexyl-3-isopropyl-3(3-nitrophenyl)-3a,6a-dihydropyrrolo(3,4-c)pyrazole-4,6(3*H*,5*H*)-dione

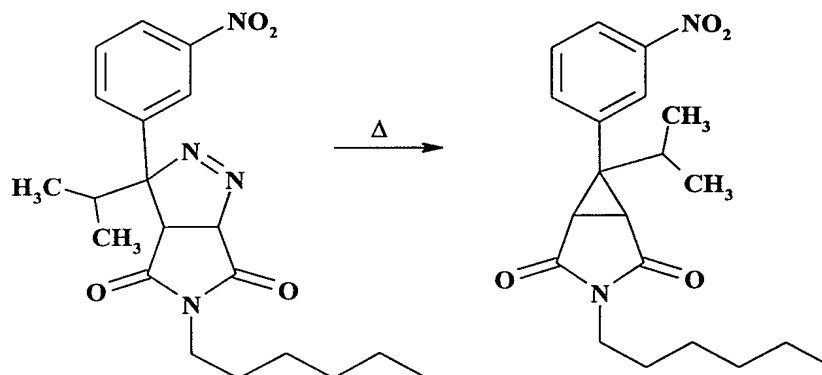
10



2-Methyl-1-(3-nitrophenyl)-1-propanone hydrazone (Preparation 57, 0.52 g, 2.5 mmol) was dissolved in dioxan (10 ml) and manganese dioxide (grade CMD-1 from Sumitomo, 5.2 g, 60.0 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 20 minutes. This solution was filtered over a pad of Celite<sup>®</sup> dropwise, directly into a solution of 1-hexyl-1*H*-pyrrole-2,5-dione (Preparation 56, 0.54 g, 3.0 mmol) in dioxan (10 ml). The Celite<sup>®</sup> pad was washed with dioxan (40 ml) to ensure complete addition of the reactants and then the reaction mixture was stoppered and stirred for 72 h.

20 The reaction mixture was purified by chromatography using a Biotage Flash 40S<sup>™</sup> cartridge packed with silica gel (40g), eluting with petroleum ether : ethyl acetate (4 : 1). The title compound was obtained as a yellow solid (0.65 g, 67%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 - 1.4 (m, 15H), 1.8 (m, 2H), 2.7 (m, 1H), 3.1 - 3.25 (m, 3H), 5.85 (d, 1H), 7.6 (m, 2H), 8.2 (m, 2H).

Preparation 593-Hexyl-6-isopropyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

5

5-Hexyl-3-isopropyl-3-(3-nitrophenyl)-3a,6a-dihydropyrrolo(3,4-c)pyrazole-4,6(3*H*,5*H*)-dione (Preparation 58, 0.65 g, 1.6 mmol) was dissolved in dioxan (25 ml) and heated under reflux for 3 h. The solvent was removed *in vacuo* and the oily residue dried in vacuum for 16 h at room temperature to give the crude product as a yellow solid. The crude product

10

was purified by chromatography on a Biotage Flash 12M<sup>TM</sup> cartridge packed with silica gel (8 g), eluting with hexane : ethyl acetate (9:1) to give the title compound (0.60 g, 100%).

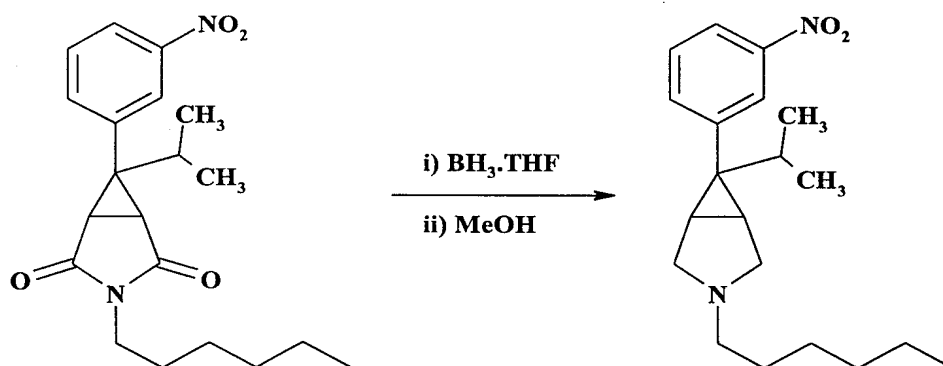
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 0.95 (d, 6H), 1.2 - 1.4 (m, 6H), 1.55 (m, 2H), 1.7 (m, 1H), 2.8 (s, 2H), 3.45 (m, 2H), 7.5 (t, 1H), 7.65 (d, 1H), 8.2 (m, 2H).

15

MS (TSP) : M/Z (MNH<sub>4</sub><sup>+</sup>) 376.4; C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> + NH<sub>4</sub><sup>+</sup> requires 376.2.

Preparation 603-Hexyl-6-isopropyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane

205



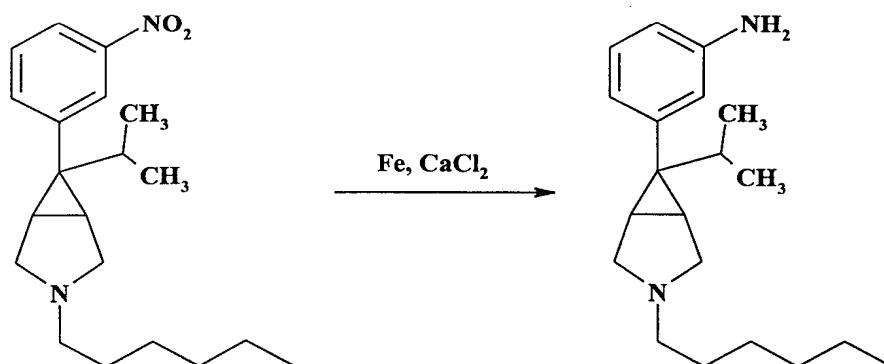
To a stirred solution of 3-hexyl-6-isopropyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 59, 0.57 g, 1.6 mmol) in tetrahydrofuran (6 ml), under nitrogen, was added borane tetrahydrofuran complex (1M in tetrahydrofuran, 3.0 ml, 3.0 mmol) and the reaction mixture was heated under reflux for 2 h. The reaction mixture was cooled to room temperature before the addition of further borane tetrahydrofuran complex (1M in tetrahydrofuran, 3.0 ml, 3.0 mmol). After 20 min, the reaction mixture was cooled to room temperature and methanol (8 ml) was added and then the reaction mixture was once more heated under reflux for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was dried under vacuum at room temperature. The residue was treated with dichloromethane (4ml), filtered and purified by chromatography on a Biotage Flash40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with hexane : ethyl acetate (6 : 1). The title compound was obtained initially as a yellow oil which crystallised upon standing (0.2 g, 40%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 - 1.0 (m, 9H), 1.25 - 1.4 (m, 6H), 1.4 (m, 2H), 1.8 (m, 2H), 2.45 (m, 2H), 2.6 (m, 1H), 2.85 (m, 2H), 3.05 (m, 2H), 7.4 (t, 1H), 7.6 (d, 1H), 8.0 - 8.15 (m, 2H).

## Preparation 61

3-(3-Hexyl-6-isopropyl-3-azabicyclo[3.1.0]hex-6-yl)aniline

206



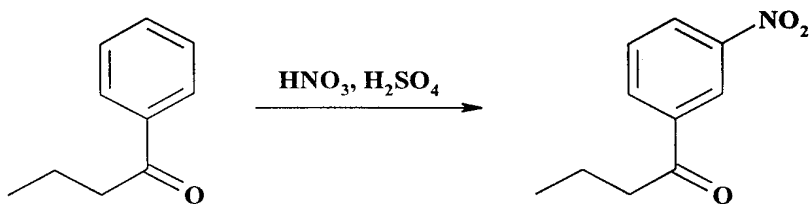
To a stirred suspension of 3-hexyl-6-isopropyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane (Preparation 60, 0.18 g, 0.54 mmol), ethanol (15 ml) and iron powder (0.27 g, 4.88 mmol) was added calcium chloride (0.06 gm 0.54 mmol) in water (3 ml). The reaction mixture was heated under reflux for 3 h and then filtered through a pad of Celite®, the mother liquors were concentrated *in vacuo*. The residue was dissolved in dichloromethane and filtered again through a Sep-Pak® Plus cartridge containing silica (1.5 g), (Water Division Millipore), to remove any residual iron salts and then concentrated to give the crude title compound as a yellow solid (0.17 g, 100%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.75 - 0.85 (m, 9H), 1.2 - 1.4 (m, 6H), 6.4 - 6.6 (m, 3H), 7.0 (t, 1H).

MS (APCI) : M/Z (MH<sup>+</sup>) 301.1; C<sub>20</sub>H<sub>32</sub>N<sub>2</sub> + H<sup>+</sup> requires 301.3.

## 15 Preparation 62

### 1-(3-Nitrophenyl)-1-butanone



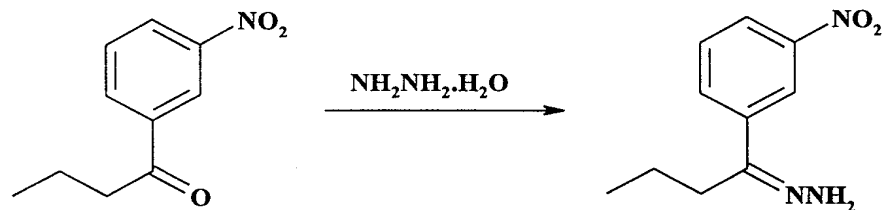
Concentrated nitric acid (40 ml) was added cautiously with cooling to concentrated sulphuric acid (100 ml) maintaining a temperature of -5°C. Another solution of butyrophenone (59.2 g, 0.47 mol) in concentrated sulphuric acid (140 ml) was made up

- with shaking, keeping the temperature at  $-5^{\circ}\text{C}$  ( $\pm 5^{\circ}\text{C}$ ). The former nitric acid/sulphuric acid solution was added portionwise over 45 min to the latter solution of ketone in sulphuric acid keeping the temperature at  $-10^{\circ}\text{C}$   $\pm 5^{\circ}\text{C}$  during the addition and for a subsequent 30 min. The reaction mixture was poured onto crushed ice (1.5 l) and then
- 5 extracted with diethyl ether (200 ml and then 3 x 100 ml). The combined organic extracts were washed with water and then aqueous saturated sodium hydrogen carbonate solution and dried ( $\text{MgSO}_4$ ) before concentrating *in vacuo*. The crude yellow oil crystallised after 16 h and was then purified by chromatography on silica gel (1 kg) eluting with hexane : diethyl ether (9 : 1) to give the title compound as a white solid (9.1 g, 10%).
- 10 NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.05 (t, 3H), 1.8 (m, 2H), 3.0 (t, 2H), 7.65 (t, 1H), 8.25 (d, 1H), 8.4 (d, 1H), 8.9 (s, 1H).

### Preparation 63

#### 1-(3-Nitrophenyl)-1-butanone hydrazone

15



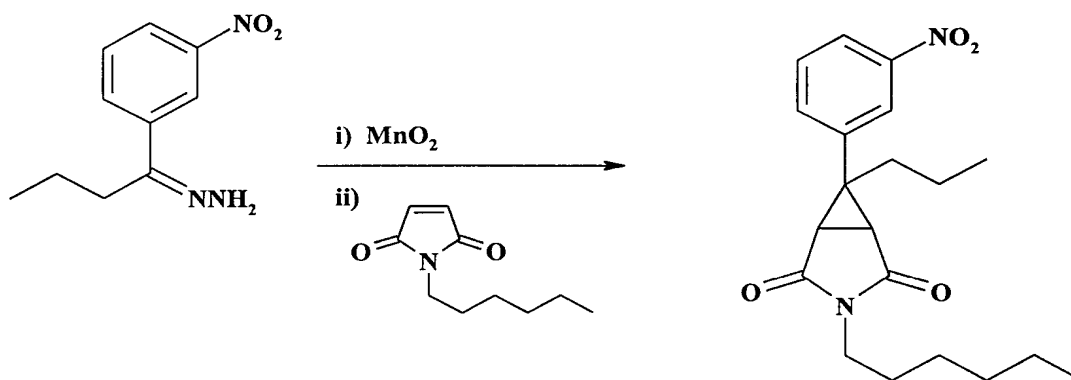
- To a partially dissolved solution of 1-(3-nitrophenyl)-1-butanone (Preparation 62, 9.0g, 46.6 mmol) in industrial methylated spirits (60 ml) was added dropwise hydrazine hydrate monohydrate (4.5 ml, 93.2 mmol). The reaction mixture was refluxed for 6 h, before
- 20 cooling to  $0^{\circ}\text{C}$  and adding water (60 ml) dropwise with stirring. The mixture was cooled in a refrigerator for 16 h and the orange crystals (7.5 g) so formed were removed by filtration. The filtrate was diluted with water (350 ml) and extracted with dichloromethane (3 x 150 ml), the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to give an
- 25 orange oil (1.8 g). Both the crystals and oil were combined to give the desired title compound (9.3 g, 96%).
- NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.1 (m, 3H), 1.6 (m, 2H), 2.6 (m, 2H), 7.5 (t, 1H), 8.0 (d, 1H), 8.1 (d, 1H), 8.5 (s, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 207.9; C<sub>10</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> + H requires 208.1.

#### Preparation 64

#### 3-Hexyl-6-(3-nitrophenyl)-6-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione

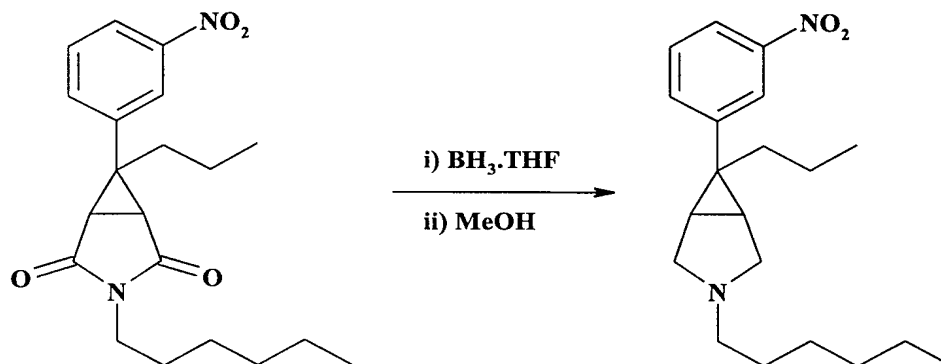
5



- 1-(3-Nitrophenyl)-1-butanone hydrazone (Preparation 63, 1.0 g, 4.8 mmol) was dissolved in dioxan (20 ml) and cooled to 10°C, manganese dioxide (grade CMD-1 from Sumitomo, 10 g, 117 mmol) was added portionwise. After the addition was complete, the reaction mixture was stirred at room temperature for 30 minutes. This suspension was filtered over a pad of Celite<sup>®</sup> directly into a solution of 1-hexyl-1*H*-pyrrole-2,5-dione (Preparation 56, 0.88 g, 4.5 mmol) in dioxan (20 ml). The Celite<sup>®</sup> pad was washed with dioxan (125 ml) and then stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* to give a crude orange oil. Methanol (8 ml) was added and the mixture was cooled to 0°C and upon scratching a white solid precipitated. The solid was filtered off and washed with cold methanol to give the pure product, the mother liquors were concentrated *in vacuo* and treated again with methanol under the procedure described above to give further product. The title compound was obtained as a white solid (0.28 g, 16%).
- NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 (m, 3H), 0.9 (m, 3H), 1.2 -1.4 (m, 8H), 1.6 (m, 2H), 1.7 (m, 2H), 2.8 (m, 2H), 3.5 (m, 2H), 7.5 (t, 1H), 7.65 (d, 1H), 8.1 (d, 1H), 8.2 (s, 1H).

#### Preparation 65

- 3-Hexyl-6-(3-nitrophenyl)-6-propyl-3-azabicyclo[3.1.0]hexane



To a stirred solution of 3-hexyl-6-(3-nitrophenyl)-6-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 64, 0.28 g, 0.78 mmol) in tetrahydrofuran (3 ml), under nitrogen, was added borane tetrahydrofuran complex (1M in tetrahydrofuran, 1.7 ml, 1.7 mmol) and the reaction mixture was heated under reflux for 2 h. The reaction mixture was cooled to room temperature, methanol (1.5 ml) was added and then the reaction mixture was heated under reflux for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in methanol (14ml) and refluxed for 5 h. The reaction mixture was concentrated *in vacuo*, methanol (14 ml) was added and the reaction mixture was refluxed for a further 3 h before concentrating *in vacuo*. The crude residue was purified by chromatography on a Biotage Flash12M<sup>TM</sup> cartridge packed with silica gel (8 g), eluting with hexane : ethyl acetate (4 : 1) to give the title compound as a yellow oil (0.2 g, 79%).

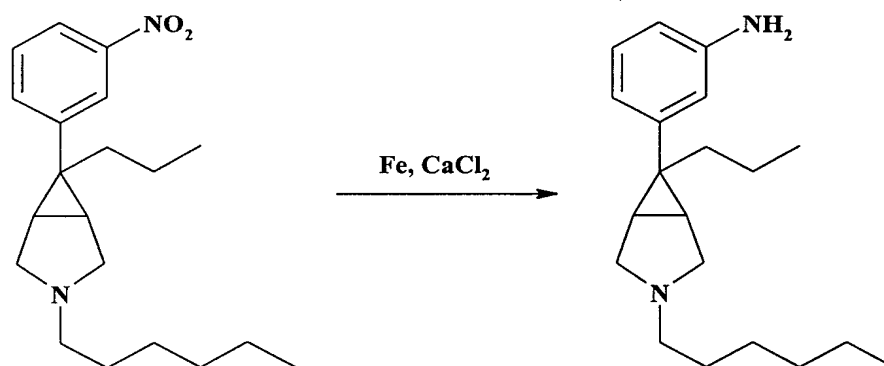
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 - 1.0 (m, 6H), 1.15 - 1.5 (m, 10H), 1.8 (m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.8 (m, 2H), 3.0 (m, 2H), 7.4 (t, 1H), 7.6 (d, 1H), 8.0 (d, 1H), 8.1 (s, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 331.1; C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> + H requires 331.2.

#### Preparation 66

#### 3-(3-Hexyl-6-propyl-3-azabicyclo[3.1.0]hex-6-yl)aniline

210



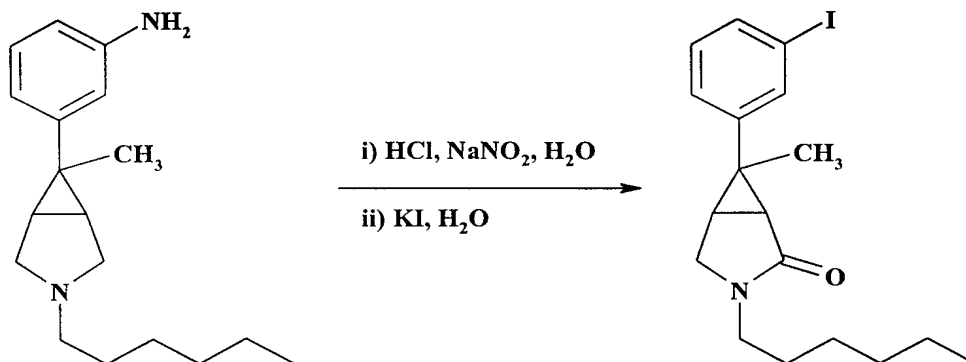
To a stirred suspension of 3-hexyl-6-(3-nitrophenyl)-6-propyl-3-azabicyclo[3.1.0]hexane (Preparation 65, 2.60 g, 7.2 mmol), ethanol (150 ml) and iron powder (0.41 g, 73.2 mmol) was added calcium chloride (1.5 g 13.0 mmol) in water (50 ml). The reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite®, and the mother liquors were concentrated *in vacuo*. The residue was dissolved in dichloromethane and filtered through a pad of sodium sulphate to give upon concentration the title compound as a yellow oil (2.17 g, 100%).

10 NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 - 1.0 (m, 6H), 1.2 - 1.4 (m, 10H), 1.6 - 1.8 (m, 4H), 2.0 (m, 2H), 2.8 (m, 2H), 3.6 (m, 2H), 6.45 - 6.55 (m, 2H), 6.6 (d, 1H), 7.0 (m, 1H).

MS (ES): M/Z (MH<sup>+</sup>) 301.2; C<sub>20</sub>H<sub>32</sub>N<sub>2</sub> + H<sup>+</sup> requires 301.3.

## 15 Preparation 67

### 3-Hexyl-6-(3-iodophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one





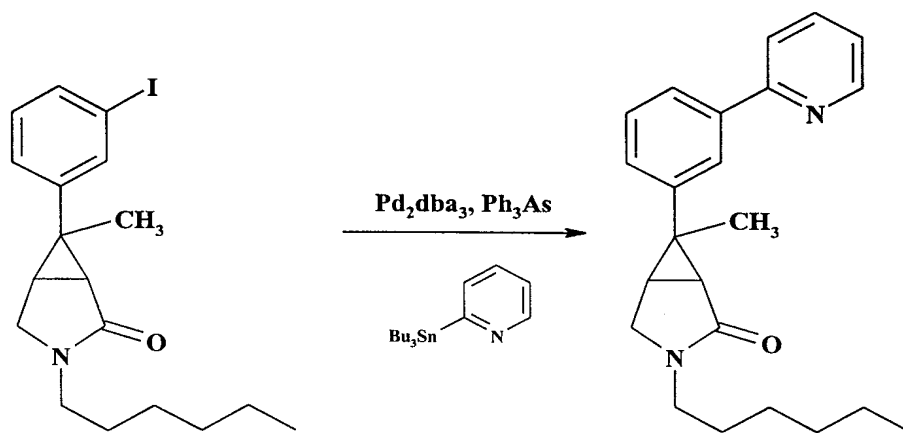
A solution of sodium nitrite (0.25 g, 3.6 mmol) dissolved in water (4 ml) was added to 3-(3-hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenylamine (Preparation 12, 0.43 g, 1.6 mmol) dissolved in aqueous hydrochloric acid (2.0 M, 4 ml) at 0°C. After 15 min at 0°C, the reaction mixture was added to potassium iodide (0.61 g, 3.69 mmol) in water (4 ml) at 0°C with rapid stirring. The reaction mixture was stirred for 30 min at room temperature and was then heated to 90°C for 5 min. The reaction mixture was cooled to room temperature and then poured cautiously onto solid sodium hydrogen carbonate with cooling. After 12 h, the reaction mixture was extracted with diethyl ether and then ethyl acetate and the combined organic extracts were washed with aqueous sodium thiosulphate solution, dried (MgSO<sub>4</sub>) and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with hexane : ethyl acetate (10 : 1 and then 3 : 1) to give the title compound (0.18 g, 24%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 9H), 1.5 (m, 2H), 2.05 (m, 1H), 2.25 (m, 1H), 3.05 - 3.3 (m, 3H), 3.65 (m, 1H), 7.0 (t, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.65 (s, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 398.1; C<sub>18</sub>H<sub>24</sub><sup>129</sup>INO + H<sup>+</sup> requires 398.1.

#### Preparation 68

##### 3-Hexyl-6-methyl-6-[3-(2-pyridinyl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one



To *tris*(dibenzylideneacetone)dipalladium (0) (4.4 mg, 4.80 μmol) in tetrahydrofuran (1 ml) at room temperature was added triphenylarsine (5.9 mg, 19.2 μmol). After 5 min, 2-

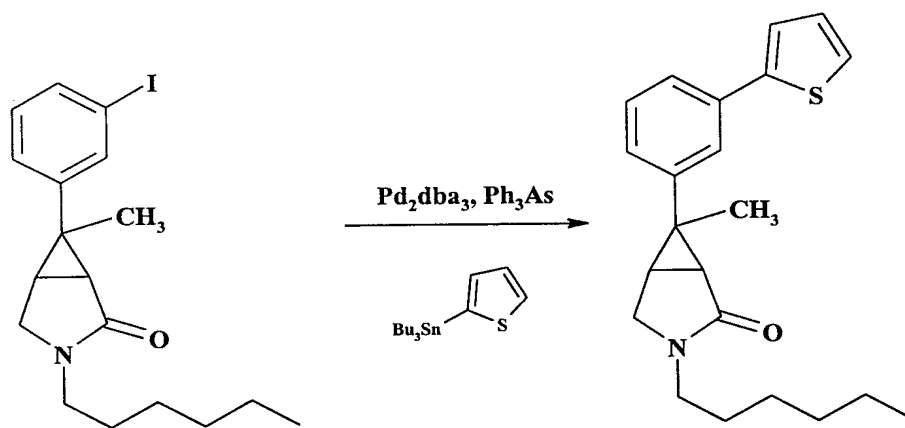
(tributylstannyl)pyridine (0.10 g, 0.29 mmol) in tetrahydrofuran (1 ml) was added followed by 3-hexyl-6-(3-iodophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 67, 77 mg, 0.19 mmol) in tetrahydrofuran (1 ml). The reaction mixture was stirred at room temperature for 16 h and then refluxed for 2 h. The cooled reaction mixture was concentrated *in vacuo* and chromatographed on silica gel eluting with hexane : ethyl acetate (1 : 1 then 0 : 1) to give the title compound as a colourless oil (67 mg, 100%).

NMR (CDCl<sub>3</sub>, selected data for the free base) : 0.9 (m, 3H), 1.2 - 1.4 (m, 6H), 1.5 - 1.7 (m, 5H), 2.1 (m, 1H), 2.4 (m, 1H), 3.1 - 3.4 (m, 3H), 3.7 (m, 1H), 7.2 - 7.3 (m, 2H), 7.35 - 7.45 (m, 2H), 7.65 - 7.85 (m, 2H), 8.0 (m, 1H), 8.7 (m, 1H).

MS (TSP) : M/Z (MH<sup>+</sup>) 348.9; C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O + H requires 349.2.

#### Preparation 69

#### 3-Hexyl-6-methyl-6-[3-(2-thienyl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one



To *tris*(dibenzylideneacetone)dipalladium (0) (4.5 mg, 4.91 μmol) in tetrahydrofuran (1 ml) at room temperature was added triphenylarsine (5.9 mg, 19.2 μmol). After 5 min, 2-(tributylstannyl)thiophene (0.10 g, 0.27 mmol) in tetrahydrofuran (1 ml) was added followed by 3-hexyl-6-(3-iodophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 67, 78 mg, 0.19 mmol) in tetrahydrofuran (1 ml). The reaction mixture was stirred at room temperature for 16 h and then refluxed for 2 h. The cooled reaction mixture was concentrated *in vacuo* and chromatographed on silica gel eluting with hexane : ethyl acetate (2 : 1) to give the title compound as a colourless oil (68 mg, 98%).

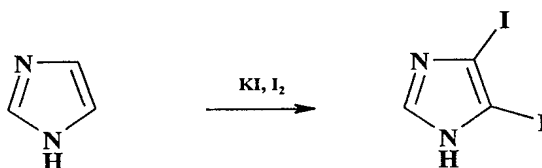
NMR ( $\text{CDCl}_3$ , selected data for the free base) : 0.9 (m, 3H), 1.2 - 1.4 (m, 9H), 1.5 (m, 2H), 2.15 (m, 1H), 2.4 (m, 1H), 3.1 - 3.4 (m, 3H), 3.7 (m, 1H), 7.05 (m, 1H), 7.2 - 7.35 (m, 4H), 7.45 (d, 1H), 7.55 (s, 1H).

MS (TSP) :  $M/Z$  ( $\text{MH}^+$ ) 354.2;  $\text{C}_{22}\text{H}_{27}\text{NOS} + \text{H}$  requires 354.2.

5

#### Preparation 70

##### 4,5-Diiodo-1H-imidazole



10

A solution of iodine (22.5 g, 88 mmol) in 20% aqueous potassium iodide (150 ml) was added dropwise to a stirred solution of imidazole (3.4 g, 49 mmol) in aqueous sodium hydroxide solution (1M, 300 ml) at room temperature. After stirring for 16 h, acetic acid was added to neutralise the reaction mixture. The white precipitate formed was filtered off and washed with water before dissolving in ethanol and concentrating *in vacuo* to give the title compound (7.7 g, 54%).

15

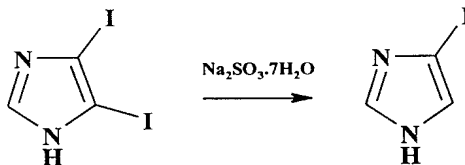
NMR ( $d_6$ -DMSO, selected data for the free base: 7.8 (br, 1H), 12.75 (br, 1H).

MS (TSP) :  $M/Z$  ( $\text{MH}^+$ ) 320.8;  $\text{C}_3\text{H}_2^{129}\text{I}_2\text{N}_2 + \text{H}$  requires 320.8.

20

#### Preparation 71

##### 4-Iodo-1H-imidazole



25

To a solution of 4,5-diiodo-1H-imidazole (Preparation 70, 7.7 g, 24 mmol) in ethanol (80 ml) and water (20 ml) was added solid sodium sulfite heptahydrate (20 g, 79 mmol). The reaction mixture was heated at reflux for 16 h, cooled, and the solid by-products were

removed by filtration. The filtrate was then concentrated *in vacuo* and the resultant solid was dried by suction. The crude residue was recrystallised from dichloromethane to give the title compound as a white solid (4.6 g, 64%).

NMR (CDCl<sub>3</sub>, selected data for the free base: 7.0 (s, 1H), 7.5 (s, 1H).

5 MS (TSP) : M/Z (MH<sup>+</sup>): 195.2; C<sub>3</sub>H<sub>3</sub><sup>129</sup>IN<sub>2</sub> + H requires 194.9.

#### Preparation 72

##### 4-Iodo-1-triphenylmethyl-1H-imidazole



10

To 4-iodo-1H-imidazole (Preparation 71, 3.0 g, 15.3 mmol) in *N,N*-dimethylformamide (25 ml) was added triphenylmethyl chloride (4.72 g, 16.9 mmol) and then triethylamine (2.5 ml, 18.4 mmol). After stirring at room temperature for 2.5 h, water (200 ml) was added and the reaction mixture was filtered and washed with water. The crude solid was chromatographed on silica gel eluting with hexane : ethyl acetate (5 : 1 and then 2 : 1). The material was then recrystallised from hexane and dichloromethane to give the title compound as a white solid (4.0 g, 59%).

15

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NMR (CDCl<sub>3</sub>, selected data for the free base: 6.9 (m, 1H), 7.0 - 7.2 (m, 6H), 7.25 - 7.4 (m, 10H).

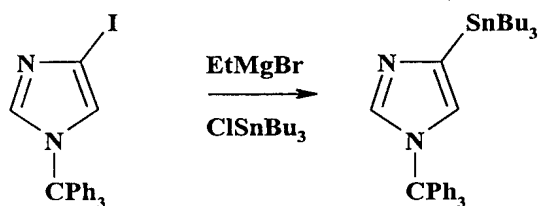
MS (TSP) : M/Z (MH<sup>+</sup>): 436.3; C<sub>22</sub>H<sub>17</sub><sup>129</sup>IN<sub>2</sub> + H requires 437.1.

#### Preparation 73

##### 4-(tributylstannyl)-1-triphenylmethyl-1H-imidazole

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215

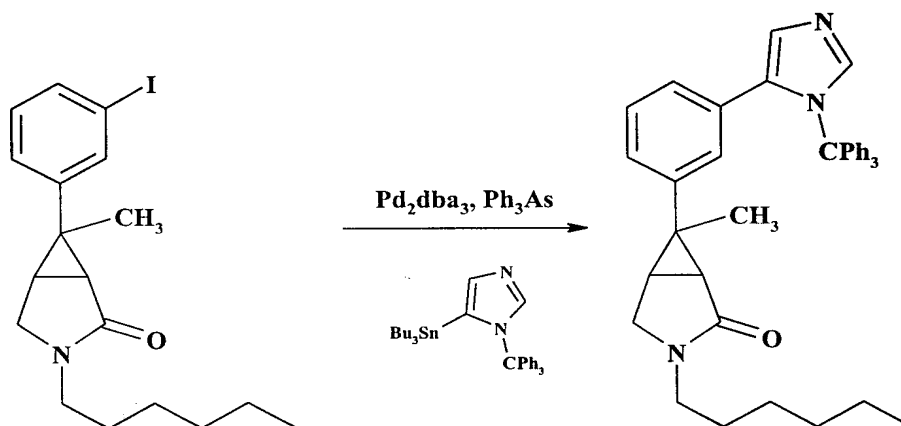


To 4-iodo-1-(triphenylmethyl)-1H-imidazole (Preparation 72, 0.44 g, 0.10 mmol) in dichloromethane (8.0 ml) at room temperature was added slowly ethyl magnesium bromide (3.0 M in diethyl ether, 0.35 ml, 1.0 mmol). After 30 min, tributyltin chloride (0.3 ml, 1.1 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml) and the product was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane : ethyl acetate (10 : 1 and then 5 : 1) to give the title compound (59 mg, 98%).

NMR ( $\text{CDCl}_3$ , selected data for the free base: 0.8 - 1.0 (m, 9H), 1.2 - 1.7 (m, 18H), 6.75 (m, 1H), 7.1 - 7.2 (m, 6H), 7.25 - 7.4 (m, 9H), 7.6 (s, 1H).

#### 15 Preparation 74

3-Hexyl-6-methyl-6-[3-(1-(triphenylmethyl)-1H-imidazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one



To *tris*(dibenzylideneacetone)dipalladium (0) (8.7 mg, 9.5  $\mu$ mol) in tetrahydrofuran (2.5 ml) at room temperature was added triphenylarsine (12 mg, 39.2  $\mu$ mol). After 10 min, a solution of 3-hexyl-6-(3-iodophenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 67, 0.15 g, 3.8 mmol) in tetrahydrofuran (2.5 ml) was added. A minute later,

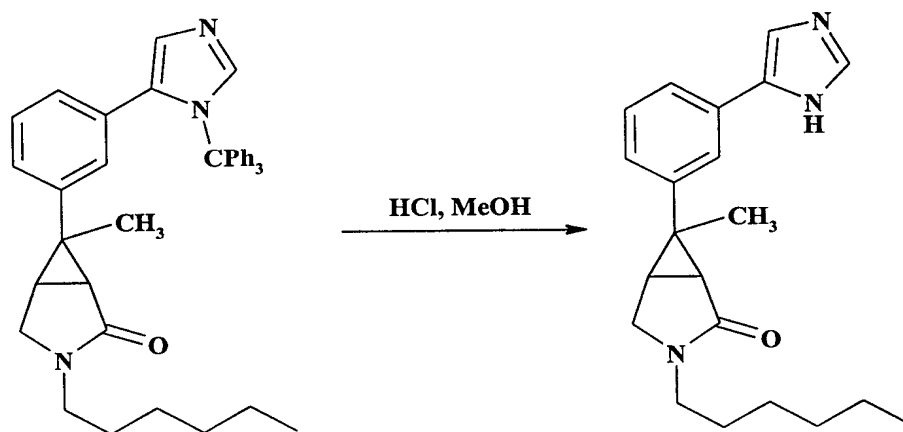
5 4-(tributylstannyl)-1-triphenylmethyl-1*H*-imidazole (Preparation 73, 0.332 g, 0.55 mmol) in tetrahydrofuran (3 ml) was added. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 3.5 h. The cooled reaction mixture was concentrated *in vacuo* and chromatographed on silica gel eluting with hexane : ethyl acetate (1 : 1 then 0 : 1) to give the title compound (55 mg, 25%).

10 NMR ( $\text{CDCl}_3$ , selected data for the free base: 0.9 (m, 3H), 1.2 - 1.4 (m, 9H), 1.5 (m, 2H), 2.15 (m, 1H), .35 (m, 1H), 3.05 - 3.4 (m, 3H), 3.65 (m, 1H), 7.1 - 7.4 (m, 18H), 7.5 - 7.6 (m, 2H), 7.75 (m, 1H).

MS (ES) :  $M/Z$  ( $\text{MH}^+$ ) 580.4;  $\text{C}_{40}\text{H}_{41}\text{N}_3\text{O} + \text{H}$  requires 580.3.

15 Preparation 75

3-Hexyl-6-[3-(1*H*-imidazol-5-yl)phenyl]-6-methyl-3-azabicyclo[3.1.0]hexan-2-one



20 To a solution of 3-hexyl-6-methyl-6-[3-(1-triphenylmethyl-1*H*-imidazol-5-yl)phenyl]-3-azabicyclo[3.1.0]hexan-2-one (Preparation 74, 55 mg, 0.95 mmol) in methanol (1.5 ml) was added aqueous hydrochloric acid (2M, 0.5 ml) and the mixture was heated under reflux for 16 h. The reaction mixture was then cooled to room temperature and poured onto solid sodium hydrogen carbonate. Dichloromethane was added, the layers were separated and

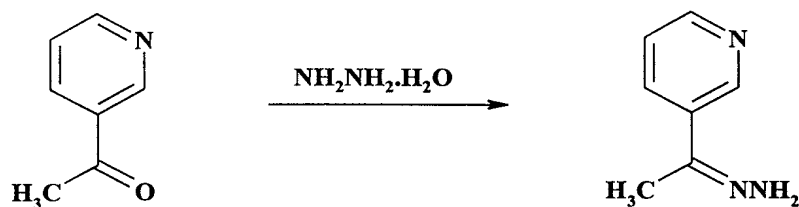
the organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The crude residue was chromatographed on silica gel eluting with ethyl acetate to give the title compound as a clear oil (21 mg, 66%).

NMR ( $\text{CDCl}_3$ , selected data for the free base: 0.9 (m, 3H), 1.2 - 1.4 (m, 9H), 1.5 (m, 2H), 2.15 (m, 1H), 2.35 (m, 1H), 3.1 - 3.4 (m, 3H), 3.7 (m, 1H), 7.2 (d, 1H), 7.3 (t, 1H), 7.35 (s, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.75 (s, 1H).

MS (ES) : M/Z ( $\text{MH}^+$ ) 338.3;  $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O} + \text{H}$  requires 338.2.

### Preparation 76

#### 10 1-(3-Pyridinyl)-1-ethanone hydrazone



To 3-acetylpyridine (6.1 g, 52 mmol) in industrial methylated spirits (50 ml) was added dropwise hydrazine hydrate monohydrate (3.11 ml, 0.1 mol). The reaction mixture was refluxed for 4 h, before cooling to room temperature and stirring for 16 h. Water (25 ml) was added and the volatile organics were removed *in vacuo*. The predominantly aqueous residual liquor was extracted with ethyl acetate, and the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give a yellow oil (5.4 g, 80%) which was taken forward without further purification.

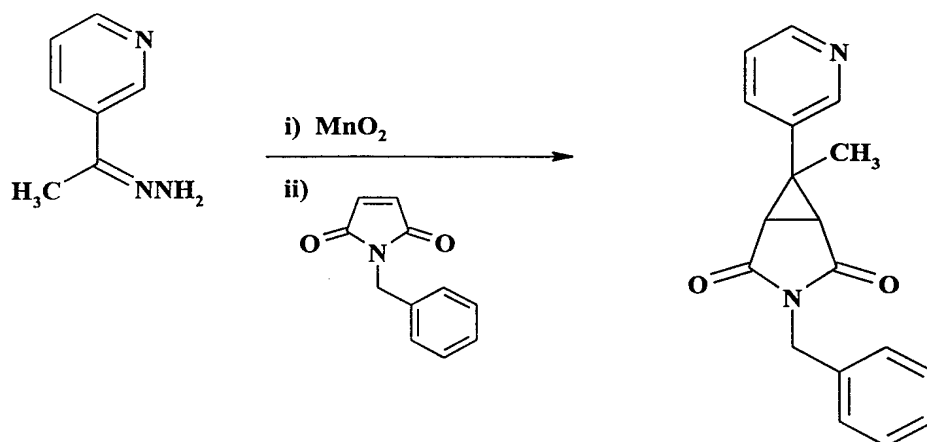
NMR ( $\text{CDCl}_3$ , selected data for the free base): 2.1 (s, 3H), 5.5 (br, 2H), 7.2 (m, 1H), 7.9 (m, 1H), 8.45 (m, 1H), 8.8 (s, 1H).

MS (ES) : M/Z ( $2\text{M}+\text{H}^+$ ) 270.7;  $\text{C}_{14}\text{H}_{19}\text{N}_6 + \text{H}$  requires 271.2.

### 25 Preparation 77

#### 3-Benzyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

218



1-(3-Pyridinyl)-1-ethanone hydrazone (Preparation 76, 5.0 g, 40.0 mmol) was dissolved in dioxan (250 ml) and manganese dioxide (6.4 g, 40.0 mmol) was added portionwise followed by a saturated solution of potassium hydroxide in ethanol (2 ml). The reaction mixture was stirred at room temperature for 4 h and then filtered through a pad of Celite®. The filtrate was added to 1-benzyl-1H-pyrrole-2,5-dione (7.5 g, 40.0 mmol) and the reaction mixture was stirred for 16 h at room temperature and was then refluxed for 72 h. The reaction mixture was concentrated *in vacuo* and the residue was suspended in methanol and filtered to give the title compound as a white solid (3 g, 25%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 1.2 (s, 3H), 2.8 (s, 2H), 4.6 (s, 2H), 7.1 - 7.6 (m, 7H), 8.4 - 8.6 (m, 2H).

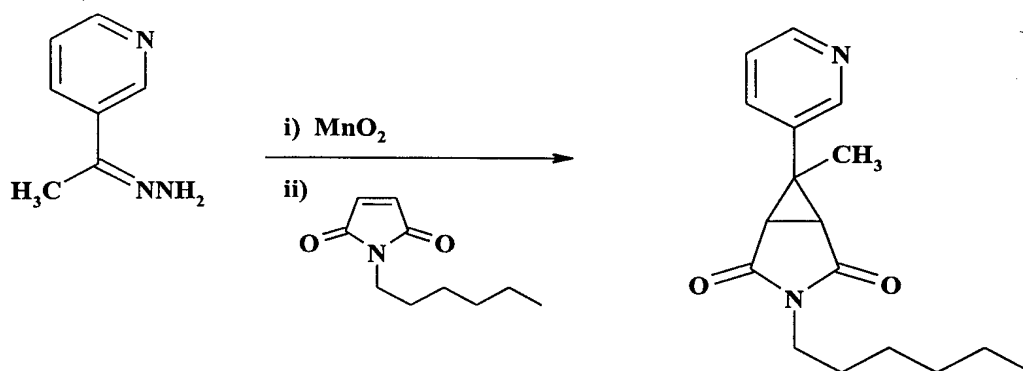
MS (TSP) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 293.0;  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2 + \text{H}$  requires 293.1.

#### 15 Preparation 78

3-Hexyl-6-methyl-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione



219



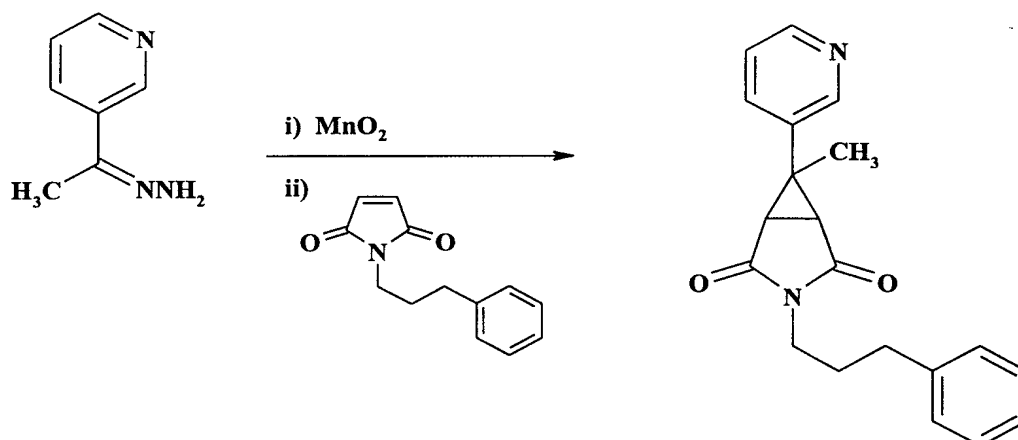
1-(3-Pyridinyl)-1-ethanone hydrazone (Preparation 76, 0.69 g, 5.3 mmol) was dissolved in dioxan (30 ml) and manganese dioxide (0.85 g, 5.3 mmol) was added portionwise followed by a saturated solution of potassium hydroxide in ethanol (0.5 ml). The reaction mixture was stirred at room temperature for 1.5 h and then filtered through a pad of Celite®. To half of the filtrate was added 1-hexyl-1*H*-pyrrole-2,5-dione (Preparation 56, 0.48 g, 2.6 mmol) and the reaction mixture was heated to 90°C for 7 h and then cooled to room temperature for 16 h. The reaction mixture was heated under reflux for 16 h and then stirred at room temperature for 72 h before concentrating *in vacuo*. The reaction mixture was purified by chromatography using silica gel (30g) eluting with dichloromethane : 0.880 ammonia (99 : 1) and then dichloromethane : methanol : 0.880 ammonia (97 : 2 : 1) to afford the title compound (0.22 g, 29%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.8 (m, 3H), 1.2 - 1.4 (m, 6H), 1.5 (s, 3H), 1.6 (m, 2H), 2.8 (m, 2H), 3.45 (m, 2H), 7.3 (m, 1H), 7.65 (m, 1H), 8.5 (m, 1H), 8.6 (m, 1H).

#### Preparation 79

6-Methyl-3-(3-phenylpropyl)-6-(3-pyridinyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

220

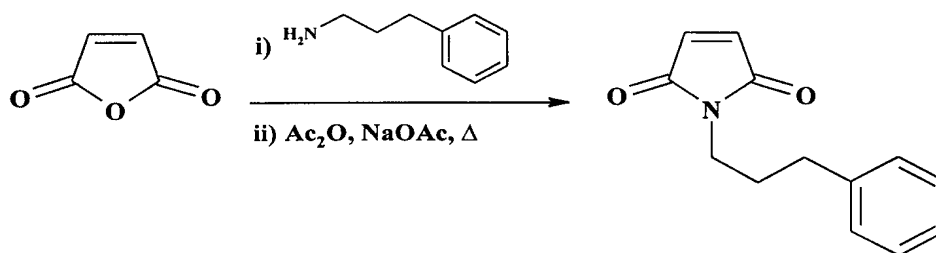


1-(3-Pyridinyl)-1-ethanone hydrazone (Preparation 76, 0.69 g, 5.3 mmol) was dissolved in dioxan (30 ml) and manganese dioxide (0.85 g, 5.3 mmol) was added portionwise followed  
 5 by a saturated solution of potassium hydroxide in ethanol (0.5 ml). The reaction mixture was stirred at room temperature for 1.5 h and then filtered through a pad of Celite®. To half of the filtrate was added 1-(3-phenylpropyl)-1*H*-pyrrole-2,5-dione (Preparation 80, 0.57 g, 2.6 mmol) and the reaction mixture was heated to 90°C for 7 h and then cooled to room temperature for 16 h. The reaction mixture was heated under reflux for 16 h and then  
 10 cooled to room temperature for 72 h before concentrating *in vacuo*. The reaction mixture was purified by chromatography using silica gel (30g) eluting with dichloromethane : 0.880 ammonia (99 : 1) and then dichloromethane : methanol : 0.880 ammonia (97 : 2 : 1) to afford the title compound as an oil (230 mg, 28%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 1.5 (s, 3H), 1.9 (m, 2H), 2.6 (m, 2H), 2.75  
 15 (s, 2H), 3.5 (m, 2H), 7.1 - 7.4 (m, 6H), 7.65 (m, 1H), 8.5 - 8.65 (m, 2H).

#### Preparation 80

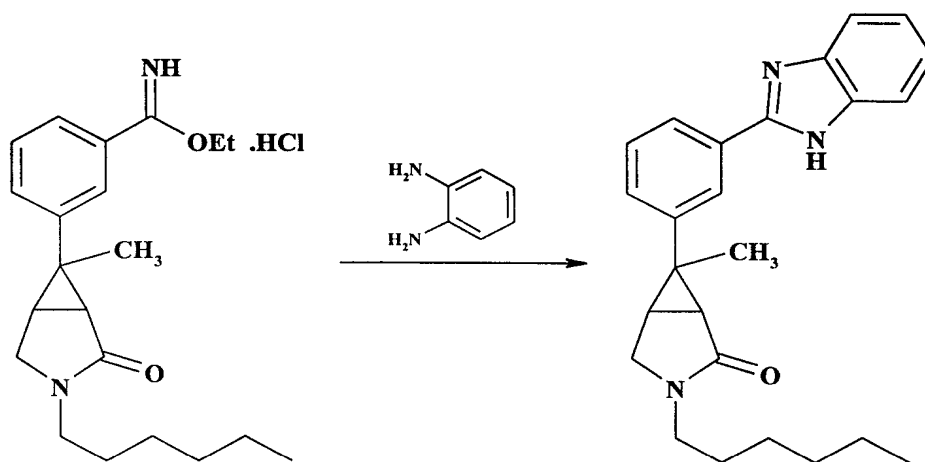
##### 1-(3-Phenylpropyl)-1*H*-pyrrole-2,5-dione



- To stirred maleic anhydride (54.4 g, 0.55 mol) in toluene (1.5 l) was added dropwise, over 1 h, 3-phenylpropylamine (79.0 ml, 0.55 mol) in toluene (500 ml) to give a pale milky solution. After 2 h, the reaction mixture was filtered and the white solid obtained was dried for 16 h *in vacuo* at 40°C. The solid was dissolved in acetic anhydride (2.0 l) with stirring and heated in a steam bath. After 10 min, sodium acetate (23 g, 0.27 mol) was added. After 4 h, the acetic anhydride was removed *in vacuo*, and the residual black solid was treated with unsaturated brine (400 ml) and extracted with ethyl acetate (3x). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate solution, followed by brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to a dark solid. The crude residue was dissolved in dichloromethane and passed through a large plug of silica gel eluting with dichloromethane to give a peach coloured solid. This solid was then recrystallised from diisopropyl ether, filtered and dried *in vacuo* at 40°C to give the title compound as a beige solid (69.6 g, 59%).
- NMR (CDCl<sub>3</sub>, selected data for the free base): 1.95 (m, 2H), 2.65 (t, 2H), 3.55 (m, 2H), 6.65 (s, 2H), 7.1 - 7.2 (m, 3H), 7.25 - 7.35 (m, 2H).
- MS (ES) : M/Z (MH<sup>+</sup>) 216; C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub> + H requires 216.

### Preparation 81

- 20 6-[3-(1H-Benzimidazol-2-yl)phenyl]-3-hexyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one



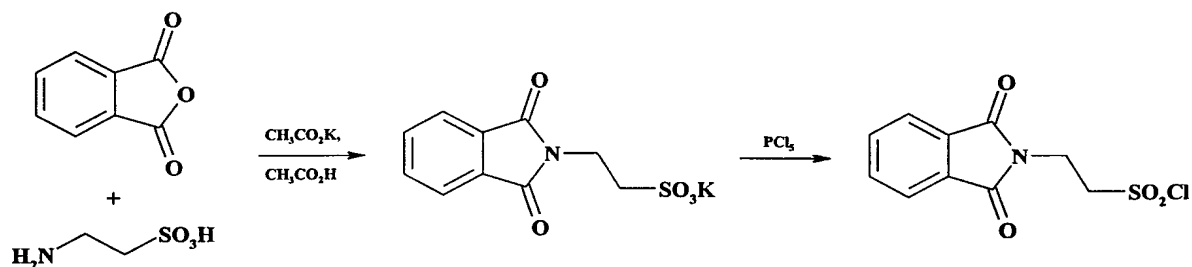
To ethyl 3-(3-hexyl-6-methyl-2-oxo-3-azabicyclo[3.1.0]hex-6-yl)benzenecarboximidoate (Preparation 42, 0.13 g, 0.34 mmol) in methanol (4 ml) at room temperature was added 1,2-diaminobenzene (37 mg, 0.34 mmol) and the mixture was heated under reflux for 1 h and then cooled and concentrated *in vacuo*. The residue was dissolved in dichloromethane (10 ml) and washed with 10% aqueous potassium carbonate solution (10 ml). The aqueous layer was then reextracted with dichloromethane (2 x 8 ml). The combined organic layers were dried (MgSO<sub>4</sub>) and then concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with hexane : ethyl acetate (1 : 1 and then 1 : 2) to give the title compound as a white foam (61 mg, 47%).

10 NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.0 (s, 3H), 1.2 - 1.4 (m, 6H), 1.5 (m, 2H), 1.8 (m, 2H), 2.1 (m, 1H), 3.05 - 3.2 (m, 2H), 3.35 (m, 1H), 3.5 (m, 1H), 7.15 - 7.35 (m, 4H), 7.6 - 7.8 (m, 3H), 8.0 (d, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 388.1 C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O + H requires 388.2.

## 15 Preparation 82

### 2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-ethanesulfonyl chloride



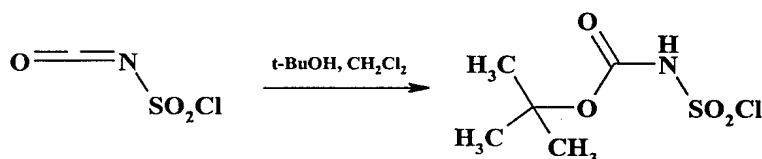
20 A suspension of taurine (8.0 g, 63.9 mmol) and potassium acetate (6.7 g, 68.3 mmol) in acetic acid was refluxed for 15 min. Phthalic anhydride (10.1 g, 68.4 mmol) was added and the solution was refluxed for 3 h. The reaction was cooled to room temperature and the solid was filtered off, washed with cold acetic acid and dried under vacuum at 100°C to give a white solid. The solid (14.3 g, 54.7 mmol) was suspended in toluene (50 ml) and

25 phosphorus pentachloride (8.12 g, 39.0 mmol) was added under nitrogen. The reaction mixture was heated under reflux for 1 h. Further phosphorus pentachloride (8.12 g, 39.0 mmol) was added and the reaction mixture was refluxed for 2.5 h. The brownish solution

was decanted from the small amount of solid formed and then concentrated *in vacuo*, the residue was poured onto ice : water (50:50, 100ml) and filtered. The solid was dried for 16 h *in vacuo* at 45°C to give a pale brown solid (6.4 g, 34%).

## 5 Preparation 83

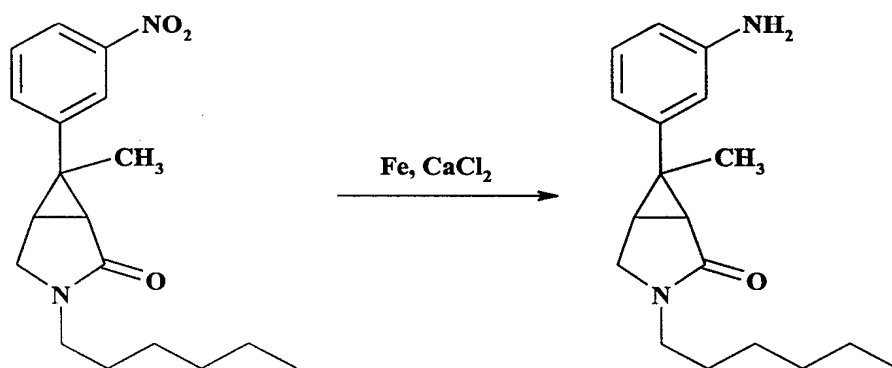
[(*tert*-Butoxycarbonyl)amino](chloro)dioxo- $\lambda^6$ -sulfane



- 10 To a solution of chlorosulphonyl isocyanate (2.4 g, 17.0 mmol) in dry dichloromethane (10 ml) stirred under nitrogen at 0°C, was added *tert*-butanol (2.2 g, 34.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h before the solvent was removed *in vacuo* to give a fluffy white solid.

## 15 Preparation 84

6-(3-Aminophenyl)-3-hexyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one



- 20 3-Hexyl-6-methyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexan-2-one (Preparation 11, 6.3 g, 19.9 mmol) was dissolved in ethanol (250 ml), and iron powder (8.5 g, 0.15 mol), calcium chloride (0.95 g, 8.6 mmol) and water (50 ml) was added. The reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and calcium

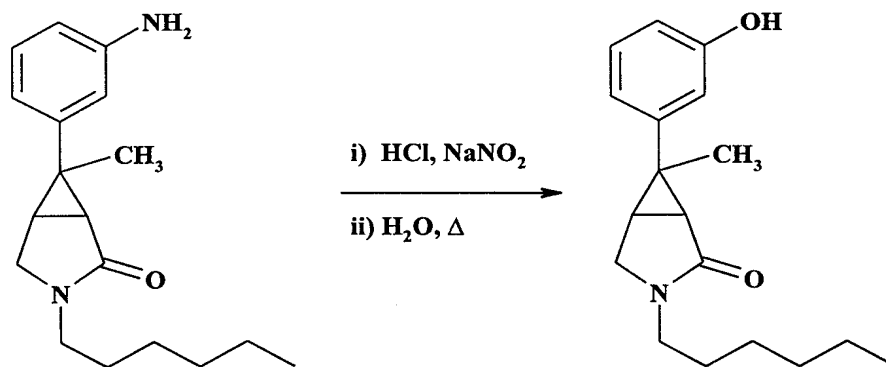
chloride (0.95 g, 8.6 mmol) was added, the reaction mixture was refluxed for a further 16 h. The reaction mixture was cooled and filtered and then concentrated *in vacuo*, the residue was partitioned between dichloromethane and water and the organic layer separated, the aqueous layer was extracted with dichloromethane (3 x) and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The title compound was obtained as an orange solid (5.72 g, 100%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 9H), 1.4 - 1.6 (m, 2H), 2.05 (m, 1H), 2.3 (m, 1H), 3.1 - 3.3 (m, 3H), 3.6 - 3.7 (m, 2H), 6.5 (d, 1H), 6.6 - 6.7 (m, 2H), 7.05 (t, 1H).

MS (ES): M/Z (MH<sup>+</sup>) 287.1 C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O + H requires 287.2

#### Preparation 85

##### 3-Hexyl-6-(3-hydroxyphenyl)-6-methyl-3-azabicyclo[3.1.0]hexan-2-one



6-(3-Aminophenyl)-3-hexyl-6-methyl-3-azabicyclo[3.1.0]hexan-2-one (Preparation 84, 1.0 g, 3.5 mmol) was dissolved in aqueous hydrochloric acid (2.5 M, 3.5 ml) and cooled to 0°C. Sodium nitrite (0.25 g, 3.6 mmol) dissolved in water (1 ml) was added to the reaction mixture and stirred for 30 min. The reaction mixture was neutralised with solid sodium carbonate and then diluted with water (5 ml). The reaction mixture was heated to 60°C for 1 h during which time a dark brown oil formed on top of the aqueous layer. The product was extracted with dichloromethane (50 ml), and the organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a brown oil. The crude product was purified by

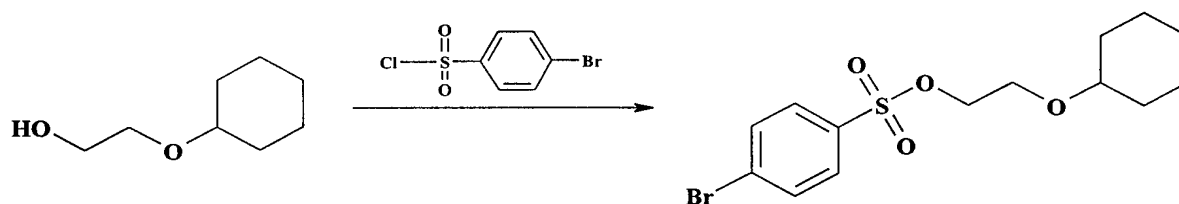
chromatography on silica gel (20 g) eluting with ethyl acetate : hexane (1 : 1) to give the title compound (0.34 g, 34%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.85 (m, 3H), 1.2 - 1.4 (m, 9H), 1.4 - 1.6 (m, 2H), 2.1 (m, 1H), 2.4 (m, 1H), 3.1 - 3.4 (m, 3H), 3.65 (m, 1H), 6.7 - 6.8 (m, 2H), 6.9 (s, 1H), 7.15 (t, 1H).

MS (ES) : M/Z (MH<sup>+</sup>) 288.2; C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub> + H requires 288.2.

### Preparation 86

#### 2-Cyclohexyloxyethyl 4-bromobenzenesulfonate



To a solution of 2-cyclohexyloxy-1-propanol (4.0 g, 28 mmol) in triethylamine (5.8 ml) and dichloromethane (250 ml) was added 4-bromobenzenesulfonyl chloride (7.87 g, 31 mmol) at 0°C under nitrogen, and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate solution, water and brine (100 ml each), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the crude product. This was purified by silica (200 g) column chromatography using a gradient elution of hexane : ethyl acetate (6 : 1 to 1 : 1) to give the title compound as a white crystalline solid (8.0 g, 80%).

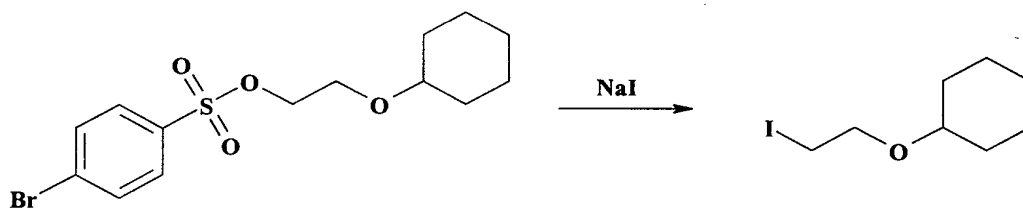
NMR (CDCl<sub>3</sub>) : 1.1-1.8 (m, 14H), 3.2 (m, 2H), 3.65 (t, 2H), 4.15 (t, 2H), 7.6-7.9 (m, 4H).

MS (thermospray) : M/Z [MH<sup>+</sup>] 362.9; C<sub>14</sub>H<sub>19</sub><sup>79</sup>BrO<sub>4</sub>S + H requires 363.0.

### Preparation 87

#### 2-Cyclohexyloxy-1-iodoethane

226

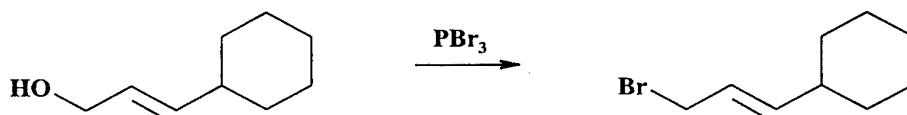


To a solution of 2-cyclohexyloxyethyl 4-bromobenzenesulfonate (Preparation 86, 120 mg, 0.3 mmol) in acetone (5 ml) was added sodium iodide (90 mg, 0.6 mmol) and the reaction mixture was left to stir at room temperature for 18 h. A further equivalent of sodium iodide was added and the reaction mixture was stirred at room temperature for a further 18 h after which time the reaction mixture was heated to 80°C for 5 h. The resulting precipitate was filtered and the filtrate was diluted with water (100 ml) and extracted with dichloromethane (100 ml). The extract was washed with brine (100 ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound as a colourless oil (50 mg, 60%).

NMR (CDCl<sub>3</sub>) : 1.1-1.9 (m, 11H), 3.1 (t, 2H), 3.7 (t, 2H).

#### Preparation 88

##### 1-[(E)-3-bromo-1-propenyl]cyclohexane



To a stirred solution of (E)-3-cyclohexyl-2-propen-1-ol (A. G. M. Barrett *et al*, Tetrahedron, 1996, 52, 15325), (1.47 g, 10.5 mmol) in diethyl ether (20 ml) and pyridine (1 ml) was added phosphorus tribromide (1.40 ml, 15 mmol) dropwise at room temperature under an atmosphere of nitrogen. After 16 h, the reaction mixture was carefully poured onto ice water (100 ml) and extracted with diethyl ether (100 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the crude product. This was purified by silica (20 g) column chromatography eluting with hexane : ethyl acetate (4 : 1) to give the title compound as a colourless oil (1.3 g, 61%).

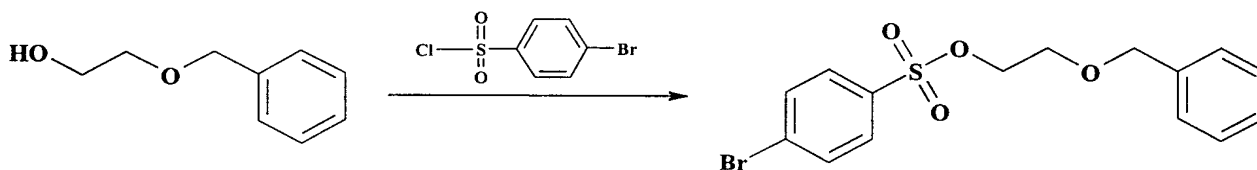


NMR (CDCl<sub>3</sub>) : 0.8-1.4 (m, 6H), 1.6-1.8 (m, 4H), 2.0 (m, 1H), 3.95 (d, 2H), 5.6-5.8 (m, 2H).

MS (thermospray) : M/Z [MH<sup>+</sup>] 203.3; C<sub>9</sub>H<sub>15</sub><sup>79</sup>Br + H requires 203.0.

## 5 Preparation 89

### (Benzyloxy)ethyl 4-bromobenzenesulfonate



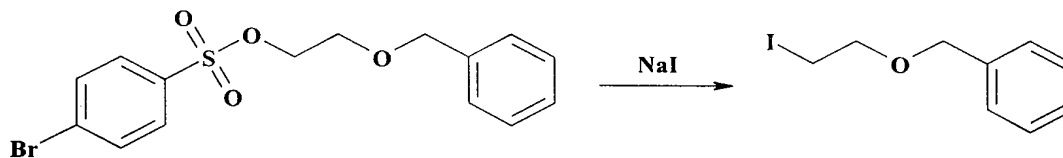
- 10 A solution of 4-bromobenzenesulfonyl chloride (5.5 g, 21.7 mmol) dissolved in dichloromethane (15 ml) was added dropwise to a solution of 2-benzyloxyethanol (3.0 g, 19.7 mmol) in triethylamine (3 g, 29.6 mmol) at 0°C under nitrogen. The resultant mixture was stirred for 16 h at room temperature. To the reaction mixture was added water (3 ml) and then the combined mixture was poured onto water (100 ml) and the product was
- 15 extracted with dichloromethane. The organic layer was washed repeatedly with water and then saturated aqueous sodium hydrogen carbonate solution, before drying (Na<sub>2</sub>SO<sub>4</sub>) and concentrating *in vacuo* to give the title compound as a white solid (6.9 g, 94%).

NMR (CDCl<sub>3</sub>) : 3.65 (m, 2H), 4.2 (m, 2H), 4.45 (s, 2H), 7.2 (m, 2H), 7.25 - 7.35 (m, 3H), 7.6 (d, 2H), 7.8 (d, 2H).

20

## Preparation 90

### 1-[(2-iodoethoxy)methyl]benzene



25

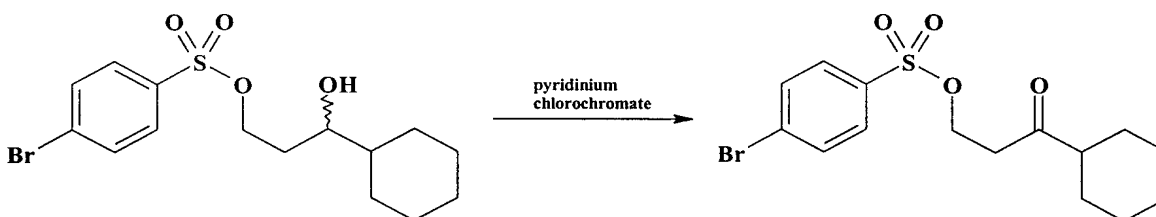
To a solution of (benzyloxy)ethyl 4-bromobenzenesulfonate (Preparation 89, 6.92 g, 19.5 mmol) in acetone (60 ml) was added sodium iodide (5.84 g, 39.0 mmol) and the reaction

mixture was left to stir at room temperature for 16 h. The resulting precipitate was filtered and the filtrate was concentrated *in vacuo*. The crude residue was dissolved in dichloromethane and washed with aqueous sodium thiosulphate solution and then with water (2 x 60 ml). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give the title compound as a pale brown oil (4.5 g, 88%).

NMR ( $\text{CDCl}_3$ ) : 3.25 (t, 2H), 3.75 (t, 2H), 4.6 (s, 2H).

### Preparation 91

#### 3-Cyclohexyl-3-oxopropyl 4-bromobenzenesulfonate



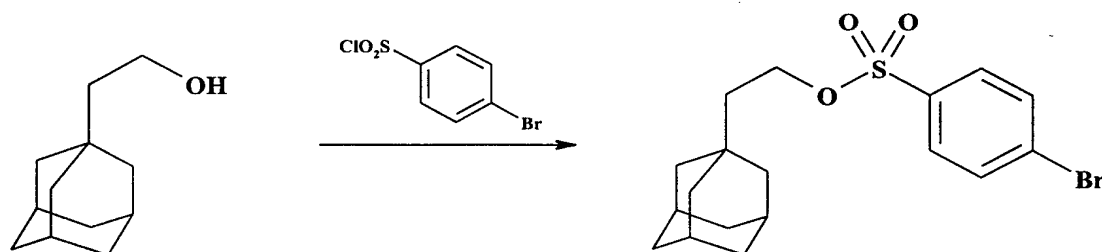
To a solution of (S)-3-cyclohexyl-3-hydroxypropyl 4-bromobenzenesulfonate (J. A. Werner *et al*, J. Org. Chem., 1996, 61, 587), (40 mg, 0.106 mmol) in dichloromethane (3 ml) was added silica (50 mg) and pyridinium chlorochromate (20 mg, 0.09 mmol), and the reaction mixture was left to stir at room temperature for 16 h. The reaction mixture was subjected to direct silica (5 g) column chromatography eluting with dichloromethane : hexane (4 : 1) to afford the title compound as a yellow solid (38 mg, 96%).

NMR ( $\text{CDCl}_3$ ) : 1.1-1.9 (m, 10H), 2.3 (m, 1H), 2.85 (m, 2H), 4.3 (m, 2H), 7.7-7.85 (m, 4H).

### Preparation 92

#### 2-Adamantylethyl 4-bromobenzenesulfonate

229



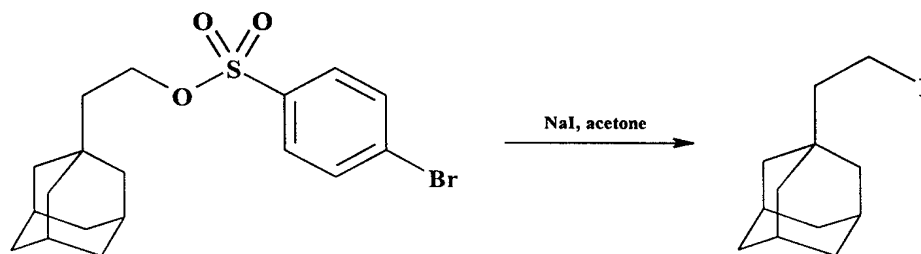
To a solution of 1-adamantylethanol (5.8 g, 32 mmol) in triethylamine (6.7 ml) and dichloromethane (50 ml) was added 4-bromobenzenesulphonyl chloride (8.9 g, 35 mmol) at room temperature. The solution was stirred for 16 h, diluted with aqueous hydrochloric acid (2M, 100 ml) and extracted with dichloromethane (100 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate solution (100 ml) and brine (100 ml), dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give the title compound as a white crystalline solid (11.2 g, 88%).

10 NMR ( $\text{CDCl}_3$ ) : 1.4-1.6 (m, 11H), 1.65 (d, 3H), 2.0 (2, 3H), 4.1 (t, 2H), 7.6-7.8 (m, 4H).

MS (thermospray) :  $\text{M/Z}$  [ $\text{MH}^+$ ] 416.3;  $\text{C}_{18}\text{H}_{23}^{79}\text{BrO}_3\text{S} + \text{NH}_4$  requires 416.1.

### Preparation 93

#### 15 1-Adamantyl-2-iodoethane



To a solution of 2-adamantylethyl 4-bromobenzenesulfonate (Preparation 92, 1.0 g, 2.5 mmol) in acetone (25 ml) was added sodium iodide (0.75 g, 5 mmol) and the reaction mixture was left to stir at room temperature for 72 h. The resulting precipitate was filtered and the filtrate was diluted with water (100 ml) and

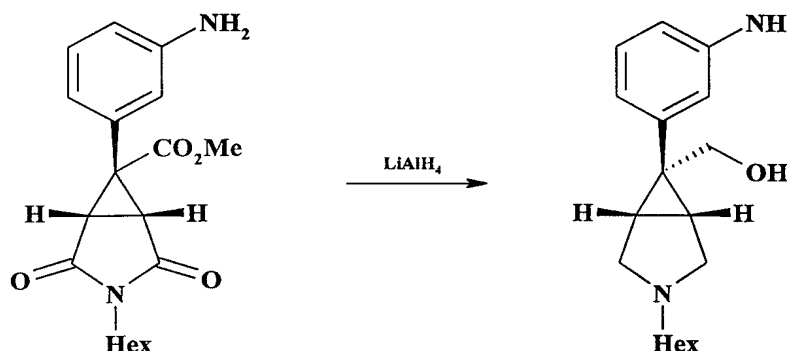
extracted with dichloromethane (100 ml). The extract was washed with brine (100 ml), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give the title compound as a white crystalline solid (0.54 g, 75%).

NMR ( $\text{CDCl}_3$ ) : 1.4-1.8 (m, 15H), 1.95 (t, 2H), 3.1 (t, 2H).

5

#### Preparation 94

#### *Exo*-[6-(3-Aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methanol



10

To a solution of methyl 6-(3-aminophenyl)-3-hexyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (Preparation 95, 25 mg, 0.0726 mmol) in anhydrous tetrahydrofuran (1 ml) at  $-10^\circ\text{C}$  under nitrogen was added lithium aluminium hydride (1M solution in tetrahydrofuran, 218  $\mu\text{l}$ , 0.218 mmol) dropwise over 10 min. The reaction was left to warm to room temperature then heated under reflux for 18 h. The cooled reaction was poured into hydrochloric acid (2M, 5 ml) then basified with aqueous sodium hydroxide (2M, 10 ml). The mixture was extracted with ethyl acetate (2 x 25 ml) and the organic layers washed with brine (25 ml), combined then dried ( $\text{MgSO}_4$ ). The organic extracts were concentrated *in vacuo* then chromatographed on Merck 230-400 silica gel (7 g) eluting with ethyl acetate : 2M ammonia in ethanol (197 : 3) to give the desired product as a colourless oil (15 mg, 71%).

20

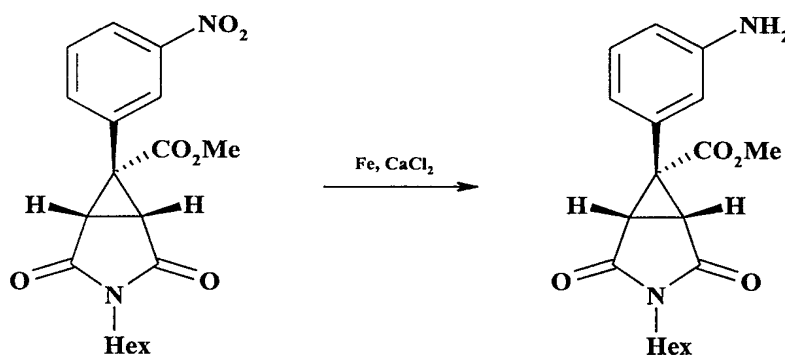
NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.20 - 1.40 (m, 6H), 1.50 (m, 2H), 1.85 (br s, 2H), 2.50 (t, 2H), 2.60 (br d, 2H), 3.40 (d, 2H), 4.10 (s, 2H), 6.50 (d, 1H), 6.60 (br s, 1H), 6.65 (d, 1H), 7.05 (dd, 1H).

MS (Thermospray) : M/Z ( $\text{MH}^+$ ) 289.1;  $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O} + \text{H}$  requires 289.4

5

### Preparation 95

#### Exo Methyl 6-(3-aminophenyl)-3-hexyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate

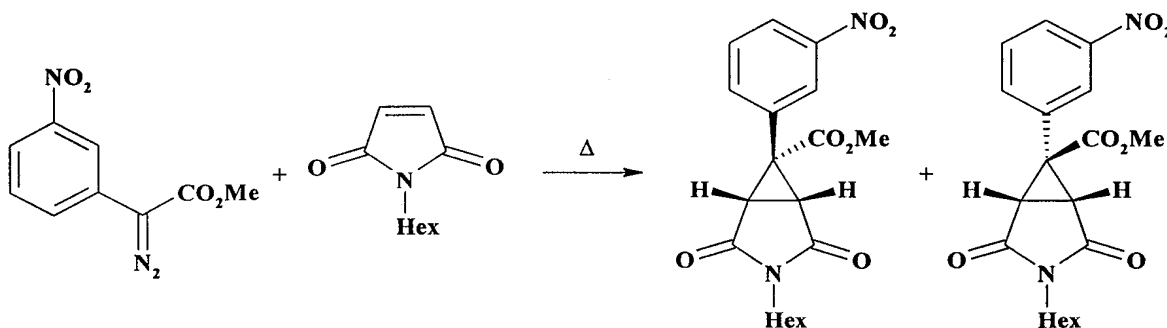


10

To a solution of methyl 3-hexyl-6-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (Preparation 96, 50 mg, 0.134 mmol) in ethanol (4.3 ml) and water (0.8 ml) was added iron powder (68 mg, 1.21 mmol) then calcium chloride (8 mg, 0.067 mmol). The reaction was heated under reflux for 6 h, cooled then filtered through Celite<sup>TM</sup> washing with ethyl acetate (50 ml). The filtrate was concentrated and the chromatographed on Merck 230-400 silica gel (10 g) eluting with ethyl acetate : hexane (40 : 60) to give the desired product as a pale yellow semi-solid (26 mg, 56%).

15 NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.25 - 1.35 (m, 6H), 1.45 (m, 2H), 2.90 (s, 2H), 3.35 (t, 2H), 3.60 (s, 3H), 6.65 (br d, 1H), 6.75 (br s, 1H), 6.80 (d, 1H), 7.10 (dd, 1H).

20 MS (Thermospray) : M/Z ( $\text{MH}^+$ ) 345.1;  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4 + \text{H}$  requires 345.4

Preparation 96*Exo* and *Endo* Methyl 3-hexyl-6-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate

5

To a stirred solution of 1-hexyl-1*H*-pyrrole-2,5-dione (Preparation 56, 123 mg, 0.678 mmol) in 1,4-dioxane (2 ml) under nitrogen was added methyl 2-diazo-2-(3-nitrophenyl)acetate (Preparation 97, 100 mg, 0.452 mmol) and the reaction mixture was heated under reflux for 48 h. The cooled mixture was concentrated *in vacuo* and the residue chromatographed on Merck 230-400 silica gel (20 g) eluting with ethyl acetate : hexane (15 : 85 and then 30 : 70) to give a mixture of two isomeric cyclopropanes (140 mg). These were separated by preparative HPLC (Condition 2), which gave in order of elution the *endo* isomer as a white solid (30 mg, 12%) some mixed fractions (40 mg, 16%) followed by the *exo* isomer as a white solid (60 mg, 24%).

15

NMR (CDCl<sub>3</sub>, selected data for the free base *endo* isomer): 0.50 (tt, 2H), 0.80 (t, 3H), 0.85 - 1.15 (m, 6H), 2.90 (t, 2H), 3.30 (s, 2H), 3.70 (s, 3H), 7.50 (dd, 1H), 7.65 (d, 1H), 8.20 (br s, 2H).

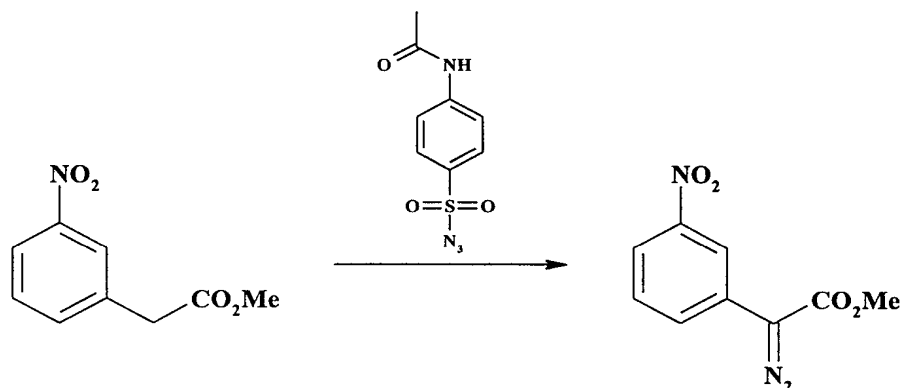
20 MS (electrospray) : M/Z (MH<sup>+</sup>) 375; C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub> + H requires 375

NMR (CDCl<sub>3</sub>, selected data for the free base *exo* isomer): 0.90 (m, 3H), 1.25 - 1.35 (m, 6H), 1.50 (m, 2H), 3.00 (s, 2H), 3.40 (t, 2H), 3.70 (s, 3H), 7.60 (dd, 1H), 7.80 (d, 1H), 8.20 (br d, 1H), 8.30 (br s, 1H).

MS (Electrospray) : M/Z (MH<sup>+</sup>) 375; C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub> + H requires 375

Preparation 97Methyl 2-diazo-2-(3-nitrophenyl)acetateUK-388510

5

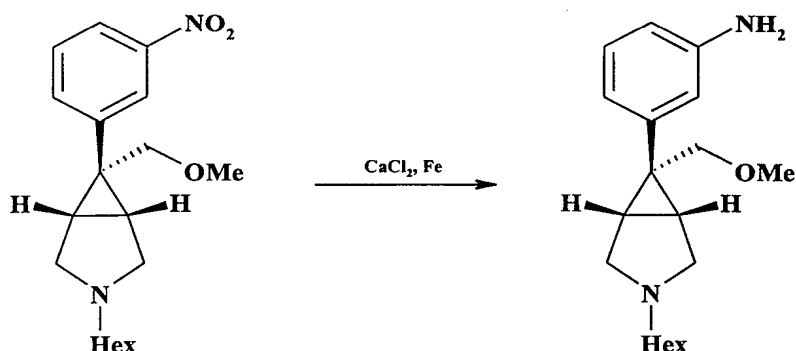


To a solution of methyl 2-(3-nitrophenyl)acetate (C. Abell *et al*, J. Chem. Soc., Perkin Trans. 1, 1994, 1997; 3.13 g, 16.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.18 ml, 7.31 g, 48.0 mmol) in anhydrous acetonitrile (35 ml), was added a solution of 4-acetamidobenzenesulphonyl azide (4.81 g, 20.0 mmol) in anhydrous acetonitrile (5 ml) in one portion. The reaction mixture was stirred for 48 h at room temperature under nitrogen before pouring into water (300 ml). The resultant precipitate was collected by filtration and washed with water (50 ml) and cold methanol (50 ml) to give the desired product as an orange/yellow solid (2.60 g, 74%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 3.90 (s, 3H), 7.60 (dd, 1H), 7.85 (br d, 1H), 8.00 (br d, 1H), 8.40 (br s, 1H).

20 Preparation 98Exo-3-[3-Hexyl-6-(methoxymethyl)-3-azabicyclo[3.1.0]hex-6-yl]aniline

234



To a solution of [3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl methyl ether (Preparation 99, 16 mg, 0.048 mmol) in ethanol (1.5 ml) and water (0.3 ml) was added iron powder (25 mg, 0.435 mmol) then calcium chloride (3 mg, 0.24 mmol). The reaction mixture was heated under reflux for 6 hours, cooled then filtered through Celite™ washing with ethyl acetate. The filtrate was concentrated *in vacuo* and chromatographed on Merck 230-400 mesh silica gel (7 g) eluting with ethyl acetate : hexane : 2M ammonia in hexane (50 : 49 : 1 and then 99 : 0 : 1) to give the desired product as a pale yellow oil (11 mg, 76%).

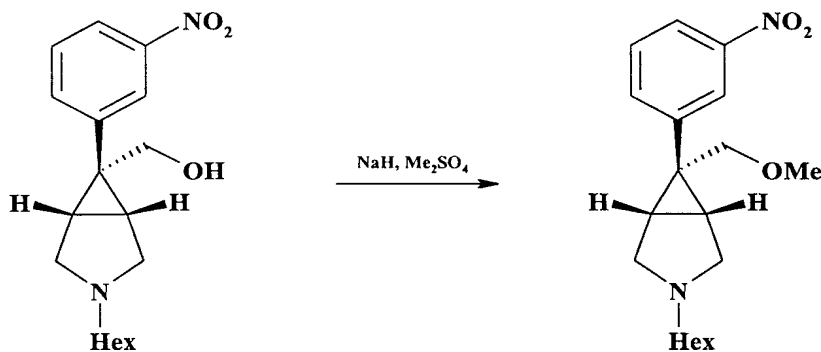
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.90 (m, 3H), 1.20 - 1.50 (m, 8H), 1.85 (br s, 2H), 2.45 (t, 2H), 2.70 (br d, 2H), 3.20 (d, 2H), 3.30 (s, 3H), 4.05 (s, 2H), 6.50 (br d, 1H), 6.70 (br s, 1H), 6.75 (d, 1H), 7.05 (dd, 1H).

MS (Thermospray) : M/Z (MH<sup>+</sup>) 303; C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O + H requires 303

15

### Preparation 99

Exo-[3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl methyl ether





To sodium hydride (60% oil dispersion washed with anhydrous pentane, 13 mg, 0.320 mmol) under nitrogen was added a solution of [3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methanol (Preparation 100, 51 mg, 0.160 mmol) in anhydrous tetrahydrofuran (1 ml) dropwise over 10 minutes. The reaction was stirred for 1 h at room temperature, cooled in an ice-water bath and dimethylsulphate (18  $\mu$ l, 24 mg, 0.192 mmol) added. The reaction mixture was allowed to warm to room temperature slowly and then stirred at room temperature for 16 h, before quenching by dropwise addition of water (5 ml). The reaction mixture was partitioned between ethyl acetate (25 ml) and sodium carbonate (25 ml). The separated aqueous layer was extracted with ethyl acetate (25 ml) and the organic extracts were washed with brine (25 ml). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel eluting with ethyl acetate : hexane : 2M ammonia in ethanol (20 : 79 : 1 and then 40 : 49 : 1) to give the desired product as a pale yellow oil (16 mg, 30%).

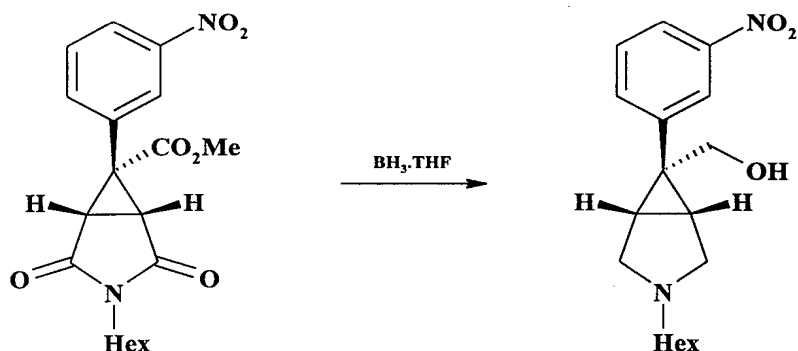
NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.25 - 1.45 (m, 8H), 1.90 (br s, 2H), 2.45 (t, 2H), 2.70 (br d, 2H), 3.20 (d, 2H), 3.30 (s, 3H), 4.15 (s, 2H), 7.40 (dd, 1H), 7.65 (d, 1H), 8.05 (br d, 1H), 8.15 (br s, 1H).

MS (thermospray) : M/Z ( $\text{MH}^+$ ) 333;  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3 + \text{H}$  requires 333

#### Preparation 100

Exo-[3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methanol

236



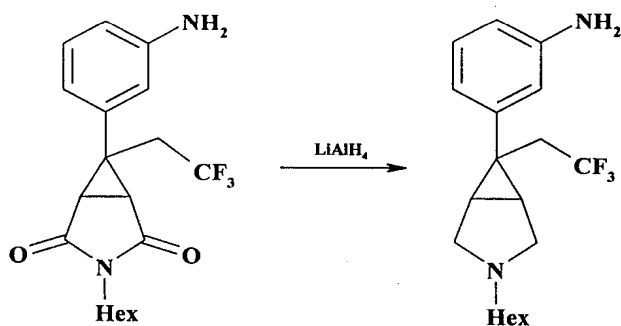
To a solution of methyl 3-hexyl-6-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (Preparation 96, 200 mg, 0.534 mmol) in anhydrous tetrahydrofuran (1ml) cooled in an ice-water bath under nitrogen was added borane (1M solution in tetrahydrofuran, 2.14 ml, 2.14 mmol) dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 1 h. The mixture was quenched by the careful addition of methanol and was then heated under reflux for 16 h. The reaction was cooled and the solvent removed *in vacuo*. More methanol was added and the mixture heated under reflux for 16 h. The solvent was again removed *in vacuo* and this process was repeated twice more. The residue was chromatographed on Merck 230-400 mesh silica gel (25 g) eluting with ethyl acetate : hexane : 2M ammonia in ethanol (40 : 59 : 1) to give the desired product as a pale yellow solid (113 mg, 66%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.90 (m, 3H), 1.20 - 1.40 (m, 6H), 1.50 (m, 2H), 1.90 (br s, 2H), 2.50 (t, 2H), 2.65 (br d, 2H), 3.45 (d, 2H), 4.20 (s, 2H), 7.45 (dd, 1H), 7.65 (d, 1H), 8.05 (br d, 1H), 8.15 (br s, 1H).

MS (thermospray) :  $\text{M/Z} (\text{MH}^+)$  319;  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3 + \text{H}$  requires 319

#### Preparation 101

3-[3-Hexyl-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hex-6-yl]aniline



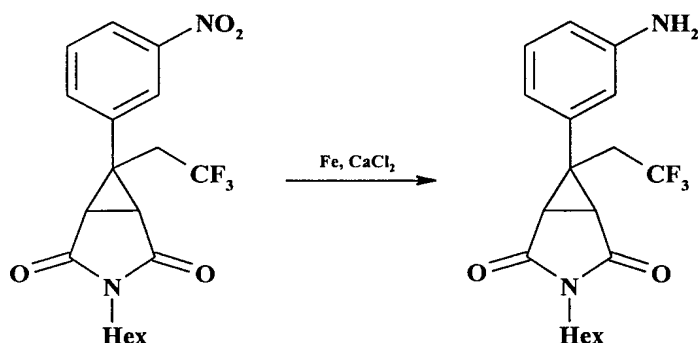
3-Hexyl-6-(3-aminophenyl)-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 102, 170 mg, 0.46 mmol) was dissolved in anhydrous tetrahydrofuran (5 ml) in a dry, nitrogen-flushed flask fitted with a thermometer and reflux condenser. The pale orange solution was cooled to  $-12^{\circ}\text{C}$  in an ice/methanol bath and lithium aluminium hydride (1M solution in tetrahydrofuran, 0.9 ml, 0.9 mmol) was added dropwise maintaining the internal temperature below  $-10^{\circ}\text{C}$ . Once the addition was completed, the red-orange mixture was allowed to warm to room temperature before heating under reflux for 1.5h. The mixture was cooled to room temperature and the residual lithium aluminium hydride quenched by the careful addition of aqueous hydrochloric acid (2M) until hydrogen evolution had ceased. The mixture was then neutralised with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (10 ml), dried ( $\text{MgSO}_4$ ), filtered and the solvents removed *in vacuo* to give the product as a pale brown gum (145 mg, 93%).

NMR ( $\text{CDCl}_3$ , selected data for the free base): 0.80-0.95 (m, 3H), 1.20-1.45 (m, 8H), 1.45-1.60 (m, 2H), 2.40 (t, 2H), 2.60 (d, 2H), 3.10 (q, 2H), 3.20 (d, 2H), 3.60 (br, 2H), 6.50 (d, 1H), 6.60 (s, 1H), 6.65 (d, 1H), 7.05 (t, 1H).

MS (electrospray) :  $\text{M/Z}$  ( $\text{MH}^+$ ) 341.4;  $\text{C}_{19}\text{H}_{27}\text{F}_3\text{N}_2 + \text{H}$  requires 341.4.

#### Preparation 102

3-Hexyl-6-(3-aminophenyl)-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione



5

3-Hexyl-6-(3-nitrophenyl)-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (Preparation 103, 178 mg, 0.45 mmol) was dissolved in ethanol (15 ml). Iron powder (225 mg, 4.0 mmol) was added at room temperature followed by calcium chloride (50 mg, 0.45 mmol), dissolved in water (2 ml). The vigorously stirred mixture was heated under reflux for 2h then cooled to room temperature and filtered through a pad of silica. The solvent was removed *in vacuo* and the filtrate was dissolved in dichloromethane and filtered through a Whatman anotop 10 plus<sup>TM</sup> cartridge. The organic mixture was concentrated *in vacuo* to give the product as a brown gum (170 mg, 100%).

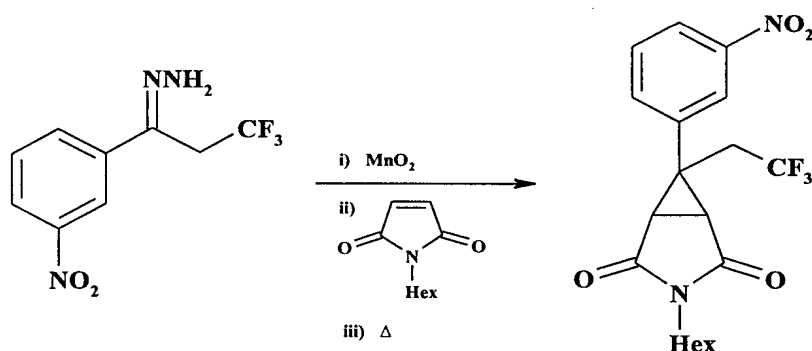
10

15 NMR (CDCl<sub>3</sub>, selected data for the free base): 0.80-0.95 (m, 3H), 1.20-1.35 (m, 6H), 1.45-1.60 (m, 2H), 2.55 (q, 2H), 2.80 (s, 2H), 3.45 (t, 2H), 2.75 (broad s, 2H), 6.55 (d, 1H), 6.65 (s, 1H), 6.70 (d, 1H), 7.10 (t, 1H).

MS (thermospray) : M/Z (MNH<sub>4</sub><sup>+</sup>) 386.5; C<sub>19</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> + NH<sub>4</sub> requires 386.4

20 Preparation 103

3-Hexyl-6-(3-nitrophenyl)-6-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

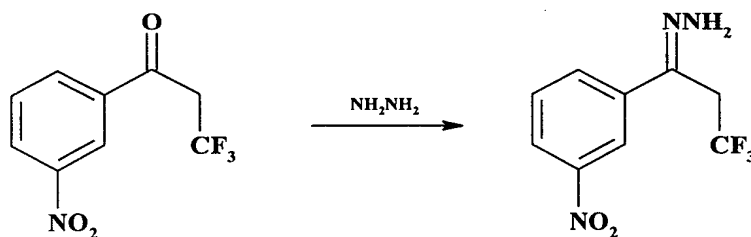


- 3,3,3-Trifluoro-1-(3-nitrophenyl)-1-propanone hydrazone (Preparation 104, 150 mg, 0.6 mmol) was dissolved in dioxan (10 ml) and manganese dioxide (600mg, 7.1 mmol) was added in one portion at room temperature. After stirring for 30 min, the reaction mixture was filtered through a pad of Arbocel™ directly into a flask containing a stirred solution of 1-hexyl-1*H*-pyrrole-2,5-dione (Preparation 56, 44 mg, 0.2 mmol) in dioxan (10 ml). The filter pad was washed further with dioxan (40 ml), and was also added to the reaction mixture. The resulting amber-yellow solution was stirred for 16 h at room temperature. The colourless mixture was then heated under reflux for 1h before cooling to room temperature and concentrating *in vacuo*. The residue was purified by chromatography on silica gel (10g), eluting with hexane : ether (2 : 1) to give the product as a white solid (178 mg, 74%).
- NMR (selected data): 0.85-0.95 (m, 3H), 1.25-1.35 (m, 6H), 1.50-1.65 (m, 2H), 2.60 (q, 2H), 2.90 (s, 2H), 3.40-3.55 (t, 2H), 7.60 (t, 1H), 7.75 (d, 1H), 8.20 (d, 1H), 8.30 (s, 1H).
- MS (APCI) : M/Z (M-H<sup>+</sup>) 397.0: C<sub>19</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> - H requires 397.4.

## Preparation 104

### 3,3,3-Trifluoro-1-(3-nitrophenyl)-1-propanone hydrazone

240



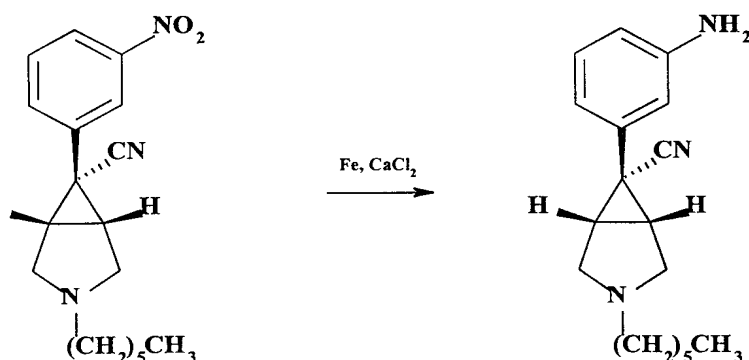
3,3,3-Trifluoro-1-(3-nitrophenyl)-1-propanone (Sov. Prog. Chem. (Engl. Transl.), 1966, 32, 745, 1.8 g, 7.72 mmol) was dissolved in tetrahydrofuran (10 ml) and  
 5 hydrazine monohydrate (0.56 ml, 11.58 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 1 h at room temperature then heated under reflux for 40 min. The reaction mixture was concentrated *in vacuo* and the residue treated with water (10 ml) and extracted with dichloromethane (4 x 10 ml). The organic extracts were concentrated *in vacuo* and the residue was  
 10 purified by chromatography on silica gel (100 g), eluting with dichloromethane : hexane (1:1 and then 2:1). The product was obtained as an amber gum (159 mg, 8%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 3.55 (q, 2H), 5.95 (br s, 2H), 7.55 (t, 1H), 8.00 (d, 1H), 8.15 (d, 1H), 8.55 (s, 1H).

15 MS (electrospray) : M/Z (M-H<sup>+</sup>) 246.1 C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub> - H requires 246.2.

### Preparation 105

#### Exo-6-(3-aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile



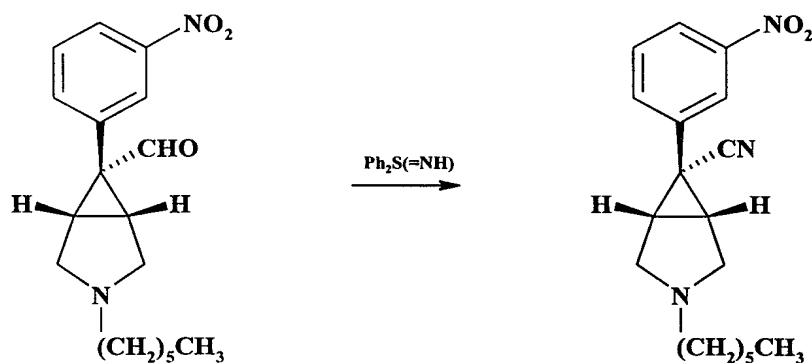
To a solution of 3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile (Preparation 106, 3 mg, 0.0096 mmol) in ethanol (1 ml) and water (0.2 ml) was added iron powder (6 mg, 0.096 mmol) then calcium chloride (0.6 mg, 0.0048 mmol). The reaction was heated under reflux for 6 h, cooled then filtered through Celite<sup>TM</sup> washing with ethyl acetate (50 ml). The filtrate was concentrated *in vacuo* to give the desired product as a pale yellow oil (1.7 mg, 63%).

NMR (CDCl<sub>3</sub>, selected data for the free base): 0.90 (m, 3H), 1.25 - 1.35 (m, 6H), 1.45 (m, 2H), 2.20 (m, 2H), 2.45 (m, 2H), 2.85 (m, 2H), 3.20 (m, 2H), 6.50 - 6.60 (m, 2H), 6.70 (br s, 1H), 7.10 (dd, 1H).

MS (thermospray) : M/Z (M<sup>+</sup>) 283.2; C<sub>18</sub>H<sub>25</sub>N<sub>3</sub> requires 283.2

### Preparation 106

15 Exo-3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile



A solution of 3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carbaldehyde (Preparation 107, 9 mg, 0.028 mmol) and diphenylsulphilimine monohydrate (12.5 mg, 0.057 mmol) in anhydrous benzene (1 ml) was heated under reflux under nitrogen for 24 hours. The solvent was removed *in vacuo* and the residue chromatographed on Merck 230-400 mesh silica gel (5 g) eluting with ethyl

acetate : hexane (30 : 70 and then 50 : 50) to give the desired product as a pale yellow oil (3 mg, 34%).

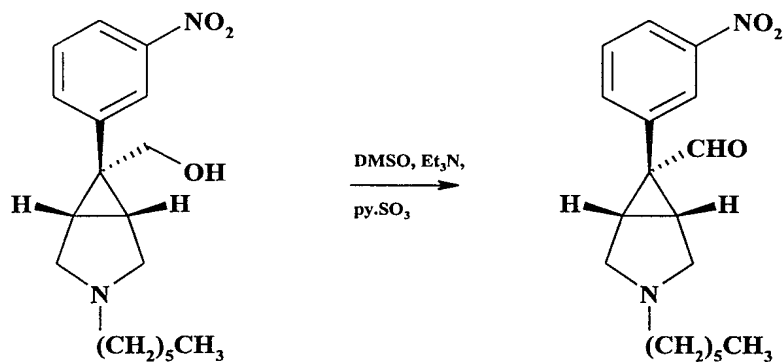
NMR (CDCl<sub>3</sub>, selected data for the free base): 0.90 (m, 3H), 1.20 - 1.45 (m, 6H), 1.50 (m, 2H), 2.25 (m, 2H), 2.55 (m, 2H), 2.80 (m, 2H), 3.35 (m, 2H), 7.5 (dd, 1H), 7.80 (d, 1H), 8.05 (br s, 1H), 8.15 (br d, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 314.2; C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> + H requires 314.2

### Preparation 107

#### Exo-3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carbaldehyde

10



15

To a solution of [3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methanol (Preparation 100, 50 mg, 0.157 mmol) in anhydrous dimethylsulphoxide (1 ml) was added anhydrous triethylamine (131  $\mu$ l, 0.941 mmol) followed by a solution of sulphur trioxide-pyridine complex (75 mg, 0.471 mmol) in anhydrous dimethyl sulphoxide (0.7 ml). The reaction mixture was stirred at room temperature for 40 h under nitrogen, before pouring into dichloromethane (25 ml) and basifying with aqueous saturated sodium bicarbonate solution (20 ml). The separated aqueous layer was extracted with dichloromethane (20 ml) and the combined organic extracts were dried (MgSO<sub>4</sub>) and then concentrated *in vacuo* to give the desired product as a pale yellow oil (9 mg, 18%).

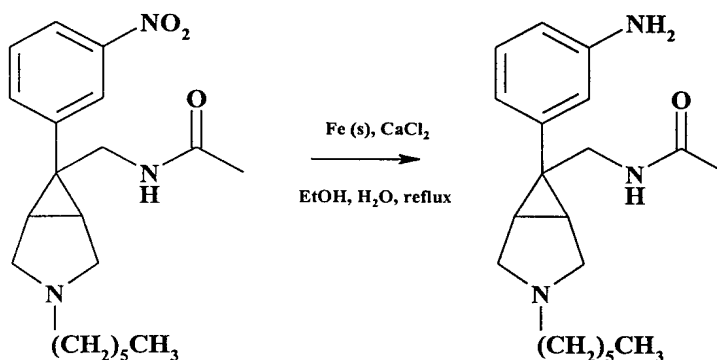
20



NMR (CDCl<sub>3</sub>, selected data for the free base): 0.90 (m, 3H), 1.20 - 1.40 (m, 6H), 1.50 (m, 2H), 2.05 (br s, 2H), 2.55 - 2.60 (m, 4H), 3.15 (d, 2H), 7.45 (dd, 1H), 7.70 (d, 1H), 8.05 (br d, 1H), 8.15 (br s, 1H), 9.40 (s, 1H).

## 5 Preparation 108

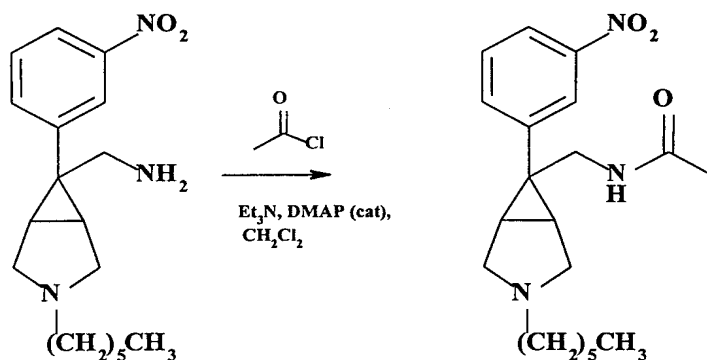
N-{[6-(3-Aminophenyl)-3-hexyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}acetamide



- 10 To a solution of N-{3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}acetamide (Preparation 109, 84 mg, 0.234 mmol) in ethanol (4 ml) and water (1 ml) was added iron powder (120 mg, 2.15 mmol) and calcium chloride (16 mg, 0.14 mmol). The mixture was stirred and heated under reflux for 1 ¼ h, before allowing to cool and filtering through Celite<sup>TM</sup>, washing with hot ethanol.
- 15 The filtrate was concentrated *in vacuo* to give a brown residue which was partitioned between dichloromethane (5 ml) and water (5 ml), leaving some insoluble material at the interface. The phases were separated and the aqueous layer was re-extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the title compound
- 20 as a golden oil (68mg, 77%).

NMR (CDCl<sub>3</sub>): 0.90 (m, 3H), 1.23-1.40 (m, 6H), 1.45 (m, 2H), 1.80-1.90 (m, 5H), 2.50 (m, 2H), 2.80 (m, 2H), 3.10 (m, 2H), 3.65 (m, 2H), 3.95 (m, 2H), 5.45 (m, 1H), 6.5 (m, 1H), 6.55-6.65 (m, 2H), 7.05 (t, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 330.3; C<sub>20</sub>H<sub>31</sub>N<sub>3</sub>O + H requires 330.3.

Preparation 109N-{3-Hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl}methyl}acetamide

5

A solution of [3-hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methylamine (Preparation 110, 80 mg, 0.234 mmol) and triethylamine (0.16 ml, 0.35 mmol) in anhydrous dichloromethane (2 ml) was stirred under nitrogen and treated with acetyl chloride (0.025 ml, 0.35 mmol) followed by 4-dimethylaminopyridine (a few crystals). The reaction mixture was stirred for 18 h at room temperature, then concentrated *in vacuo* to give a yellow solid (205 mg). The crude solid was purified by column chromatography on silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300:8:1 and then 50:8:1) to give the title compound as a yellow solid (84 mg, 100%).

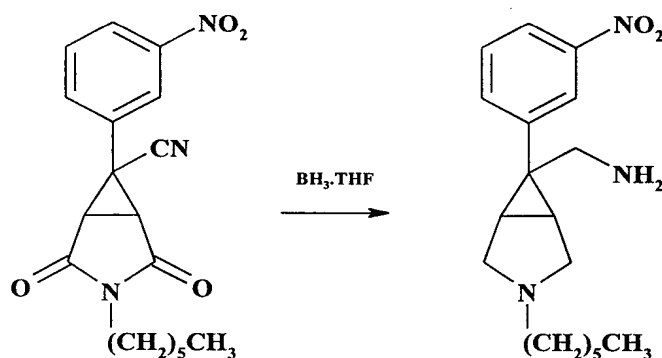
NMR (CDCl<sub>3</sub>): 0.90 (m, 3H), 1.22-1.35 (m, 6H), 1.50 (m, 2H), 1.80-1.95 (m, 5H), 2.50 (m, 2H), 2.75 (m, 2H), 3.25 (m, 2H), 4.25 (m, 2H), 5.55 (m, 1H), 7.45 (m, 1H), 7.65 (d, 1H), 8.00-8.10 (m, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 360.2; C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> + H requires 360.2.

20

Preparation 110[3-Hexyl-6-(3-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]methylamine

245



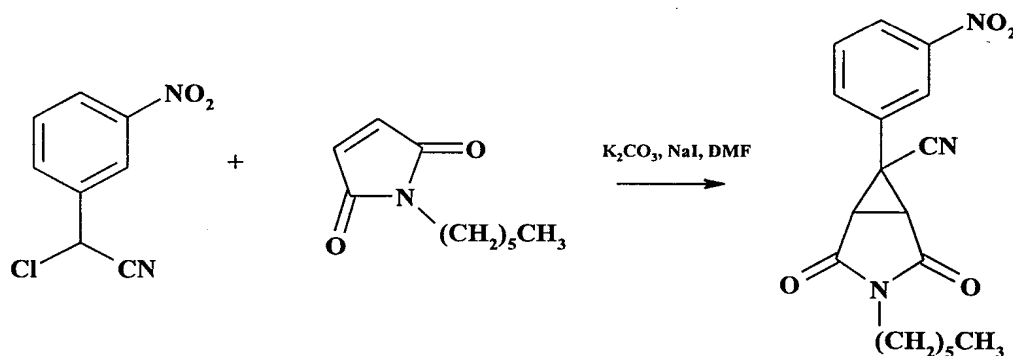
To a solution of 3-hexyl-6-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonitrile (Preparation 111, 250mg, 0.732mmol) in anhydrous tetrahydrofuran (3 ml) stirred under nitrogen was added dropwise borane-tetrahydrofuran complex (1.0M in tetrahydrofuran, 2.9 ml, 2.9 mmol). The reaction mixture was heated at reflux for 2 h, before cooling and quenching with dry methanol (2 ml). The solution in methanol was heated under reflux for 18 h before concentrating *in vacuo*. The residue was again dissolved in methanol (*ca* 5 ml) and heated at reflux for 3 hours, followed by evaporation to dryness *in vacuo*. This process was repeated once more and extensive drying gave a brown oil (270 mg) which was purified by column chromatography on silica gel (13 g) eluting with dichloromethane : ethanol : 0.88 ammonia (150 : 8 : 1). This gave the title compound as an orange oil (124 mg, 53%).

NMR (CDCl<sub>3</sub>): 0.90 (t, 3H), 1.20-1.35 (m, 6H), 1.45 (m, 2H), 1.85 (m, 2H), 2.45 (t, 2H), 2.75 (m, 2H), 3.20 (m, 2H), 3.42 (s, 2H), 7.45 (t, 1H), 7.65 (d, 1H), 8.05 (d, 1H), 8.17 (s, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 318.2; C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> + H requires 318.2.

#### Preparation 111

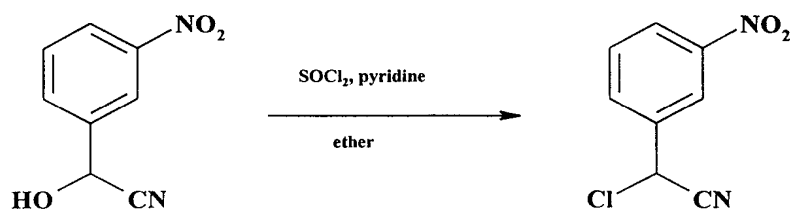
3-Hexyl-6-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonitrile



- A solution of 2-chloro-2-(3-nitrophenyl)acetonitrile (Preparation 112, 103mg, 0.524mmol) and 1-hexyl-1H-pyrrole-2,5-dione (Preparation 56, 79mg, 0.436mmol) in *N,N*-dimethylformamide (2 ml) was added dropwise over 30 min to a stirred slurry of potassium carbonate (120 mg, 0.868 mmol) and sodium iodide (33 mg, 0.22 mmol) in *N,N*-dimethylformamide (4 ml) and water (0.1 ml) at 0°C. The reaction mixture was stirred for 30 min at 0°C and then allowed to warm to room temperature. After stirring at room temperature for 2 h the mixture was diluted with water (10 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic phases were dried ( $MgSO_4$ ) and concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel eluting with hexane : ethyl acetate (5:1 and then 3:1). This gave the title compound as brown needles (47 mg, 32%).
- NMR ( $CDCl_3$ ) : 0.90 (m, 3H), 1.20-1.40 (m, 6H), 1.63 (m, 2H), 3.21 (s, 2H), 3.56 (m, 2H), 7.68 (t, 1H), 7.80 (m, 1H), 8.12 (s, 1H), 8.30 (d, 1H).

### Preparation 112

#### 2-Chloro-2-(3-nitrophenyl)acetonitrile



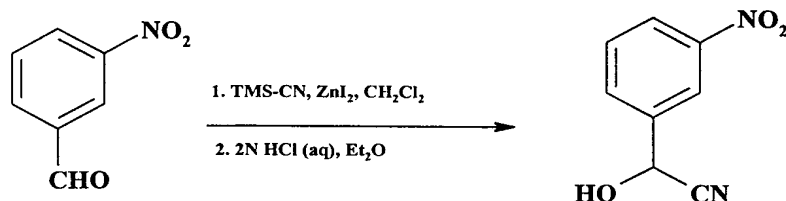
A solution of 2-hydroxy-2-(3-nitrophenyl)acetonitrile (Preparation 113, 1.0g, 5.62 mmol) in diethyl ether (10 ml) was stirred at room temperature and treated with pyridine (0.1 ml, 1.24 mmol) followed by thionyl chloride (0.82 ml, 11.2 mmol) dropwise over 5 minutes. The mixture was gently heated under reflux and after 30 min the solvent was removed by evaporation to give a pale yellow solid. This was purified by column chromatography on silica gel eluting with hexane : ethyl acetate (3:1 and then 2:1) to give the title compound as a white crystalline solid (980mg, 89%).

10 NMR (CDCl<sub>3</sub>) : 5.68 (s, 1H), 7.70 (t, 1H), 7.95 (d, 1H), 8.35 (d, 1H), 8.42 (s, 1H).

MS (electrospray) : M/Z (M<sup>+</sup>) 195.6; C<sub>8</sub>H<sub>5</sub>ClN<sub>2</sub>O<sub>2</sub> requires 196.0.

### Preparation 113

#### 15 2-Hydroxy-2-(3-nitrophenyl)acetonitrile



To a stirred solution of 3-nitrobenzaldehyde (5.0g, 33.1mmol) in dichloromethane (30 ml) at 0 °C was added trimethylsilyl cyanide (4.63 ml, 34.7 mmol). After stirring for 6 h at room temperature, zinc iodide (210 mg, 0.66 mmol) was added which caused the reaction mixture to warm and gently reflux. After 30 min, the reaction mixture was treated with hydrochloric acid (2M, 100 ml) and diethyl ether (150 ml) and stirred vigorously for 16 h. The phases were separated and the aqueous phase was further extracted with diethyl ether (3 x 100 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give

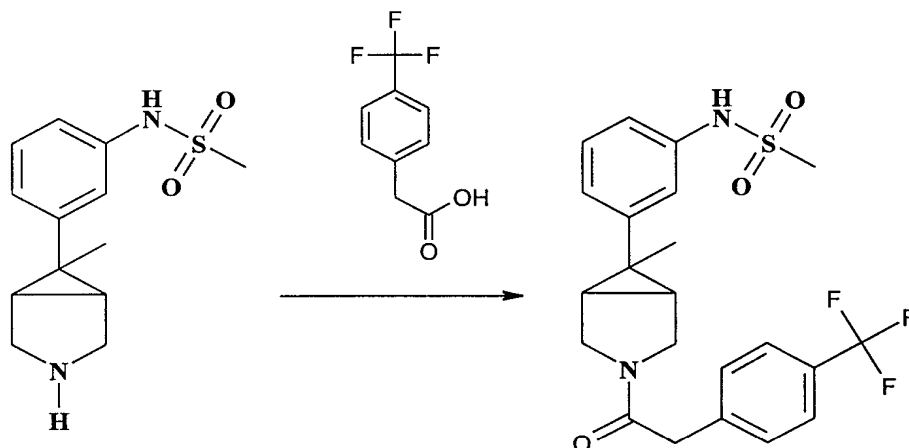
a residue which was purified by column chromatography on silica gel eluting with hexane : ethyl acetate (3:1 and then 1:1). This gave the title compound as a clear oil (5.0 g, 85%).

NMR (CDCl<sub>3</sub>) : 3.42 (br s, 1H), 5.70 (s, 1H), 7.65 (t, 1H), 7.92 (d, 1H), 8.32 (m, 1H), 8.42 (s, 1H).

MS (electrospray) : M/Z (M-H<sup>+</sup>) 177.0; C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub> - H requires 177.0.

#### Preparation 114

N-[3-(6-Methyl-3-{2-[4-(trifluoromethyl)phenyl]acetyl}-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide



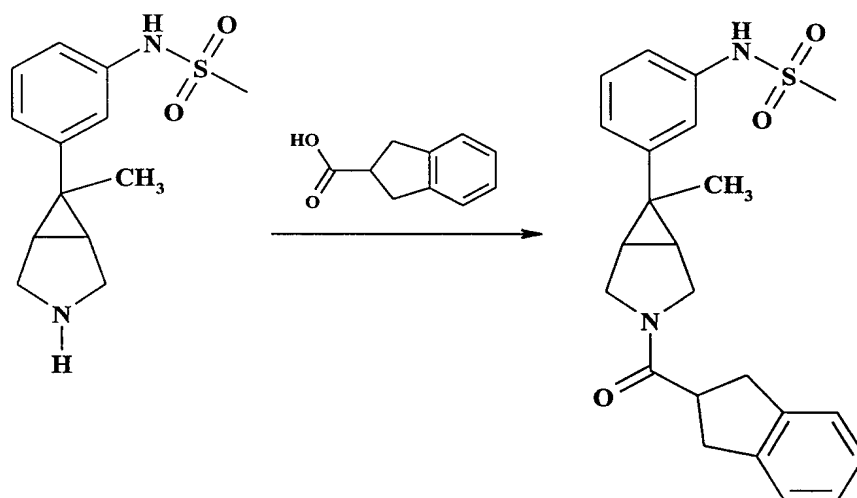
To a solution of 4-(trifluoromethyl)phenyl acetic acid (63 mg, 0.31 mmol) in *N,N*-dimethylformamide (6.5 ml) was added 1-hydroxybenzotriazole monohydrate (50 mg, 0.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (85 mg, 0.44 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 100 mg, 0.33 mmol) and sodium hydrogen carbonate (28 mg, 0.34 mmol). The reaction mixture was stirred at room temperature for 18 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate

(2 x 15 ml). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (5 g) eluting with dichloromethane : ethanol : 0.88 ammonia (200 : 8 : 1) to afford the title compound as a glassy oil (70 mg, 47%).

NMR ( $\text{CDCl}_3$ ): 1.15 (s, 3H), 1.95 (m, 2H), 3.00 (s, 3H), 3.55 - 3.90 (m, 6H), 6.45 (br. s, 1H), 7.00 - 7.15 (m, 3H), 7.25 (m, 1H), 7.40 (d, 2H), 7.60 (d, 2H).  
MS (thermospray) : M/Z ( $\text{MH}^+$ ) 452.8;  $\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 453.1.

# 10 Preparation 115

N-{3-[3-(2,3-Dihydro-1H-inden-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



15

To a solution of 2-indane carboxylic acid (E. D. Bergmann and E. Hoffmann, J. Org. Chem., 1961, 26, 3555, 100 mg, 0.62 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of N-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-

20

yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined  
 5 organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (117 mg, 43%).

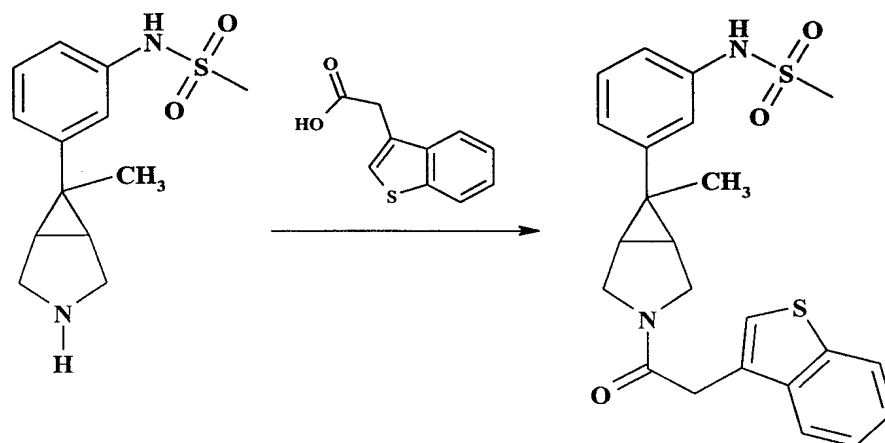
10 NMR ( $\text{CDCl}_3$ , selected data) : 1.30 (s, 3H), 2.00 (m, 2H), 3.00 (s, 3H), 3.05-3.45 (m, 5H), 3.70-3.80 (m, 3H), 3.95 (m, 1H), 6.50 (br., 1H), 7.00-7.35 (m, 8H).

MS (thermospray) : M/Z ( $\text{MH}^+$ ) 411.2;  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3\text{S} + \text{H}$  requires 411.2.

15

### Preparation 116

N-(3-{3-[2-(1-Benzothiophene-3-yl)acetyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



20



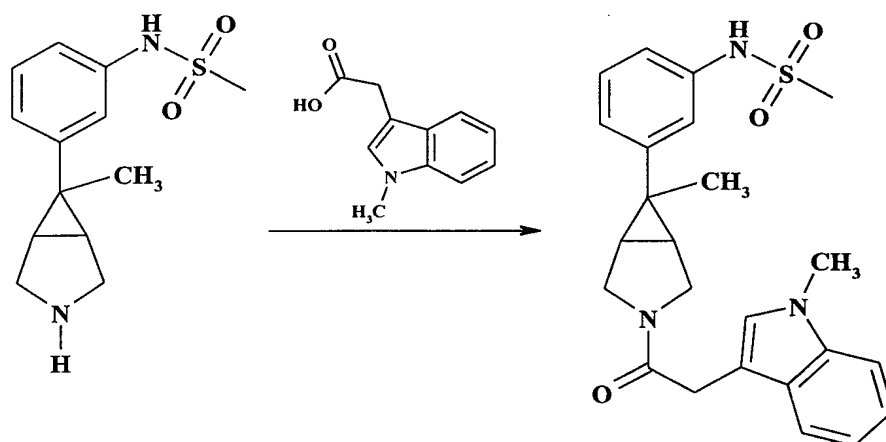
To a solution of 2-(1-benzothiophen-3-yl)acetic acid (118 mg, 0.62 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak™ cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (99 mg, 34%).

NMR (CDCl<sub>3</sub>) : 1.15 (s, 3H), 1.95 (m, 2H), 3.00 (s, 3H), 3.60 (d, 1H), 3.75-3.90 (m, 5H), 6.5 (br., 1H), 7.00-7.10 (m, 3H), 7.20-7.35 (m, 2H), 7.35-7.45 (m, 2H), 7.85 (m, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 441.1; C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 441.1.

#### Preparation 117

*N*-(3-{6-Methyl-3-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



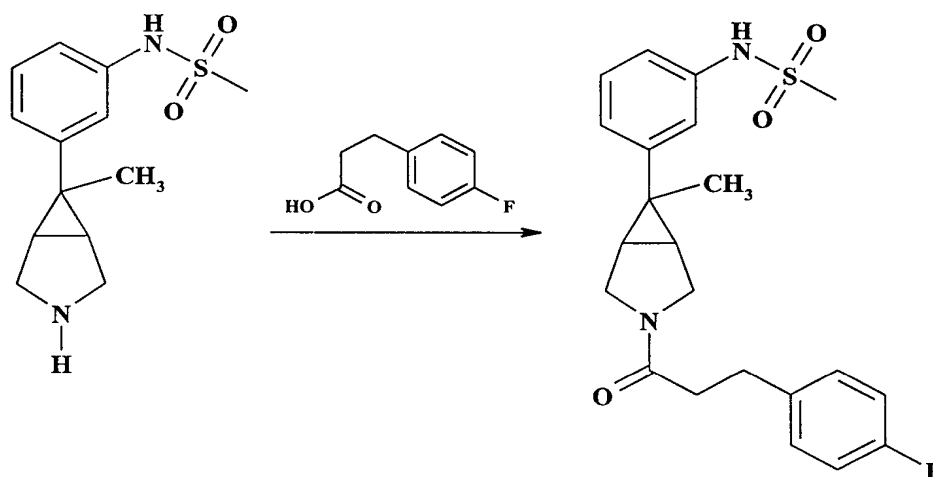
To a solution of 2-(1-methyl-1*H*-indol-3-yl)acetic acid (117 mg, 0.62 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate  
 5 (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation  
 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction  
 10 mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak™  
 15 cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (58 mg, 20%).

NMR (CDCl<sub>3</sub>, selected data) : 1.15 (s, 3H), 1.90 (br. s, 2H), 3.00 (s, 3H), 3.60-3.90 (m, 9H), 6.55 (br., 1H), 7.00-7.35 (m, 8H), 7.60 (d, 1H).

20 MS (thermospray) : M/Z (MH<sup>+</sup>) 438.2; C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 438.2

### Preparation 118

*N*-(3-{3-[3-(4-Fluorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of 3-(4-fluorophenyl)propanoic acid (104 mg, 0.62 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (100 mg, 36%).

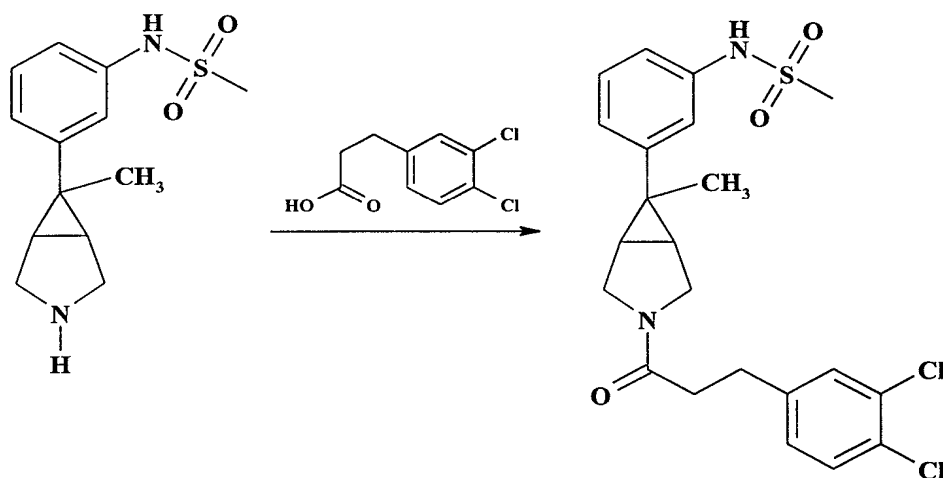
20

NMR (CDCl<sub>3</sub>) : 1.15 (s, 3H), 1.95 (m, 2H), 2.55 (m, 2H), 2.95 (m, 2H), 3.00 (s, 3H), 3.50 (d, 1H), 3.60-3.80 (m, 3H), 6.55 (br., 1H), 6.90-7.30 (m, 8H)

MS (thermospray) : M/Z (MH<sup>+</sup>) 417.3; C<sub>22</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>3</sub>S + H requires 417.2.

### Preparation 119

5 N-(3-{3-[3-(3,4-Dichlorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of 3-(3,4-dichlorophenyl)propanoic acid (35 mg, 0.16 mmol) in  
 10 *N,N*-dimethylformamide (4 ml) was added 1-hydroxybenzotriazole monohydrate  
 (26 mg, 0.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
 hydrochloride (44 mg, 0.23 mmol). After stirring at room temperature for 5 min  
 the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-  
 azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 52 mg,  
 15 0.17 mmol) and triethylamine (33 mg, 0.33 mmol). The reaction mixture was  
 stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10  
 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15  
 ml). The combined organic extracts were washed with water (10 ml) and  
 saturated brine (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give  
 20 a light brown oil. The residue was purified by chromatography using a Sep-Pak<sup>TM</sup>  
 cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol :

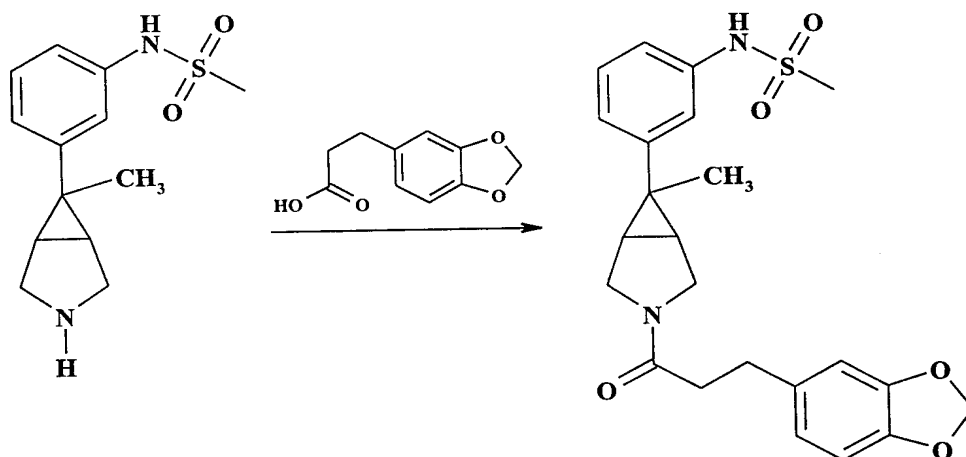
0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (38 mg, 51%).

NMR (CDCl<sub>3</sub>) : 1.20 (s, 3H), 1.95 (m, 2H), 2.55 (m, 2H), 2.95 (m, 2H), 3.00 (s, 3H), 3.50 (m, 1H), 3.70-3.80 (m, 3H), 6.50 (br., 1H), 7.00-7.15 (m, 4H), 7.20-7.40 (m, 3H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 466.8; C<sub>22</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 467.1.

### Preparation 120

N-(3-{3-[3-(1,3-Benzodioxol-5-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of 3-(1,3-benzodioxol-5-yl)propanoic acid (120 mg, 0.62 mmol) in N,N-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of N-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl)methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15

ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol :  
5 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (107 mg, 38%).

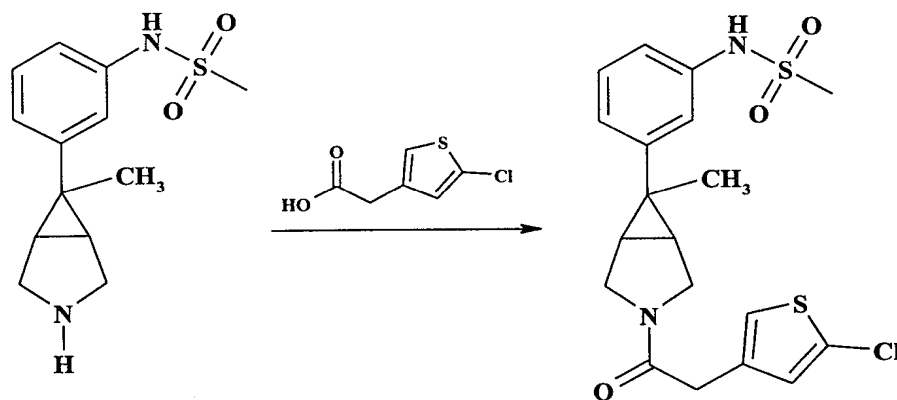
NMR ( $\text{CDCl}_3$ ) : 1.20 (s, 3H), 1.95 (br., 2H), 2.55 (m, 2H), 2.95 (m, 2H), 3.00 (s, 3H), 3.50 (m, 1H), 3.65-3.80 (m, 3H), 5.90 (s, 2H), 6.55 (br., 1H), 6.65-6.75 (m, 3H), 7.00-7.15 (m, 3H), 7.15-7.20 (m, 1H).

10 MS (thermospray) : M/Z ( $\text{MH}^+$ ) 443.2;  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5\text{S} + \text{H}$  requires 443.2.

#### Preparation 121

N-(3-{3-[2-(5-Chloro-3-thienyl)acetyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

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To a solution of 2-(5-chloro-3-thienyl)acetic acid (T. L. Cairns and B. C. McKusick, J. Org. Chem., 1950, 15, 790; 109 mg, 0.62 mmol) in *N,N*-  
20 dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-

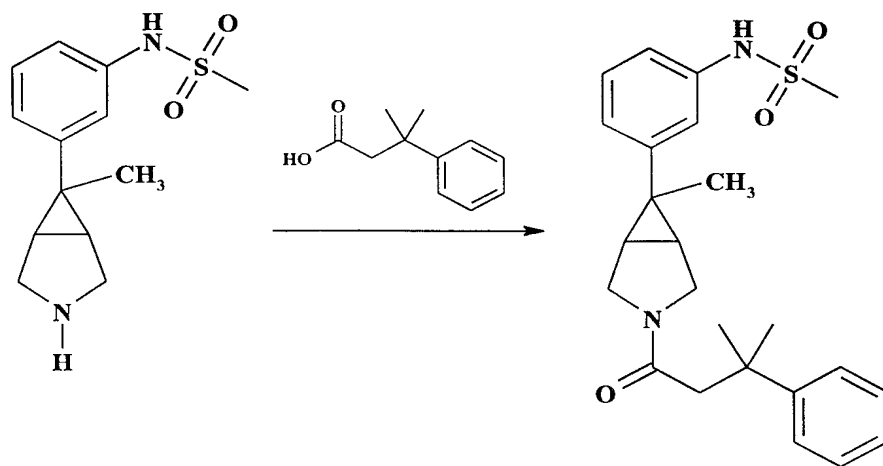
azabicyclo[3.1.0]hex-6-yl]phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.88 ammonia (250 : 8 : 1) to afford a crude product which was further purified using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (51 mg, 19%).

NMR ( $\text{CDCl}_3$ , selected data) : 1.20 (s, 3H), 2.00 (m, 2H), 3.00 (s, 3H), 3.60-3.95 (m, 6H), 6.50 (br., 1H), 6.70-6.80 (m, 2H), 7.00-7.15 (m, 3H), 7.25 (m, 1H).

MS (thermospray) : M/Z ( $\text{MH}^+$ ) 425.2;  $\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_3\text{S}_2 + \text{H}$  requires 425.1.

### Preparation 122

N-{3-[6-Methyl-3-(3-methyl-3-phenylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



To a solution of 3-methyl-3-phenylbutanoic acid (F. C. Whitmore, C. A. Weisgerber and A. C. Shabica Jr., J. Am. Chem. Soc., 1943, 65, 1469; 110 mg, 0.62 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (100 mg, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (170 mg, 0.88 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 200 mg, 0.66 mmol) and triethylamine (133 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml) and saturated brine (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a light brown oil. The residue was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.88 ammonia (250 : 8 : 1) to afford a pale yellow oil which was further purified using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white foam (70 mg, 26%).

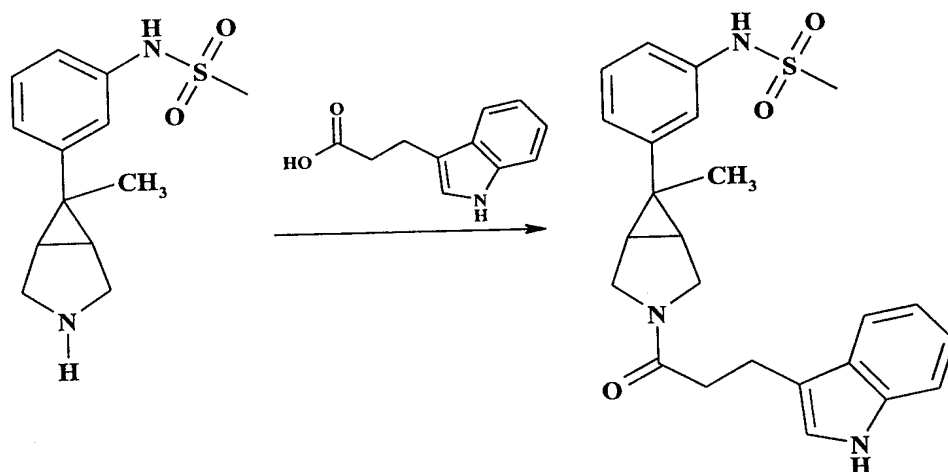
NMR (CDCl<sub>3</sub>) : 1.05 (s, 3H), 1.55 (m, 6H), 1.85 (m, 2H), 2.55 (m, 2H), 3.00 (s, 3H), 3.30-3.50 (m, 2H), 3.50-3.70 (m, 2H), 6.50 (br., 1H), 6.95-7.10 (m, 3H), 7.10-7.50 (m, 6H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 427.4; C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 427.2.

## 25 Preparation 123

*N*-(3-{3-[3-(1*H*-Indol-3-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



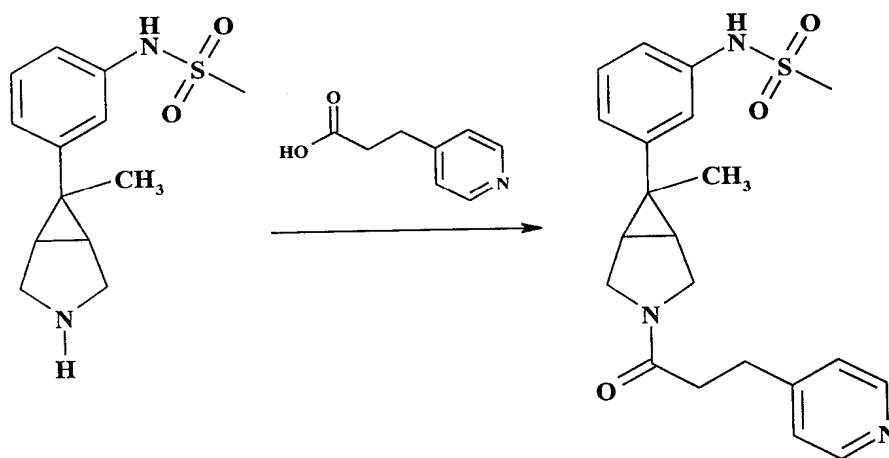


- To a solution of 3-(1*H*-indol-3-yl)propanoic acid (235 mg, 1.2 mmol) in *N,N*-dimethylformamide (13 ml) was added 1-hydroxybenzotriazole monohydrate (200 mg, 1.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.3 mmol) and sodium hydrogen carbonate (220 mg, 2.6 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (20 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 30 ml). The combined organic extracts were washed with water (20 ml) and saturated brine (20 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a pale yellow solid. The crude product was purified by shaking with dichloromethane (10 ml) and after filtration the filtrate was concentrated *in vacuo* to afford a pale yellow solid which was further purified by chromatography using a Sep-Pak<sup>TM</sup> cartridge packed with silica gel (10 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a white solid (235 mg, 43%).
- NMR (CDCl<sub>3</sub>) : 1.05 (s, 3H), 1.90 (m, 2H), 2.70 (m, 2H), 3.00 (s, 3H), 3.20 (m, 2H), 3.45 (m, 1H), 3.60-3.80 (m, 3H), 6.40 (br., 1H), 7.00-7.30 (m, 7H), 7.37 (d, 1H), 7.60 (d, 1H), 7.95 (br., 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 438.1; C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 438.2.

### Preparation 124

N-(3-{6-Methyl-3-[3-(4-pyridinyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



- To a solution of 3-(4-pyridinyl)propanoic acid (E. A. Hallinan et al., J. Med. Chem., 1996, 39, 609, 96 mg, 0.635 mmol) in *N,N*-dimethylformamide (6 ml) was added 1-hydroxybenzotriazole monohydrate (96 mg, 0.627 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (122 mg, 0.636 mmol). After stirring at room temperature for 5 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 193 mg, 0.635 mmol) and sodium hydrogen carbonate (160 mg, 1.907 mmol). The reaction mixture was stirred at room temperature for 5 d before partitioning between water (5 ml) and dichloromethane (5 ml). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a brown oil (260 mg). The residue was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge

packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.88 ammonia (300 : 8 : 1) to afford the title compound as a pink foam (100 mg, 62%).

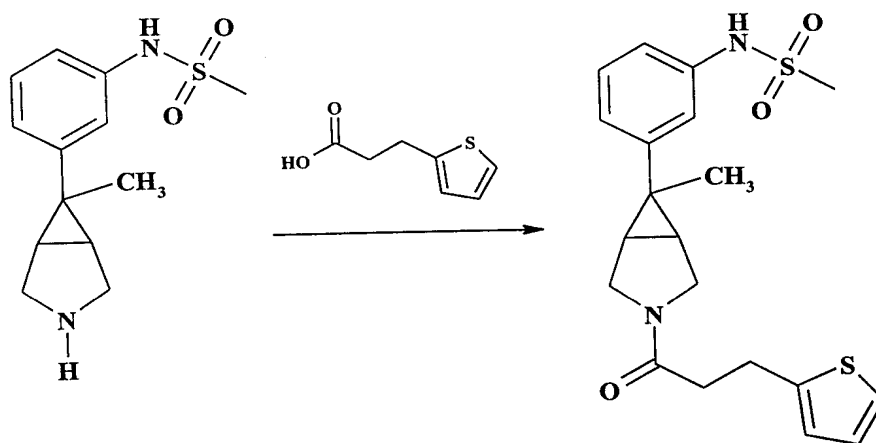
NMR (CDCl<sub>3</sub>) : 1.18 (s, 3H), 1.95 (m, 2H), 2.60 (m, 2H), 2.95-3.05 (m, 4H), 3.52 (m, 2H), 3.70-3.80 (m, 4H), 7.00-7.10 (m, 2H), 7.10-7.20 (m, 2H), 7.20-7.30 (m, 2H), 8.50 (d, 2H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 400.2; C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 400.2.

IR  $\nu_{\max}$  (polyethylene card)/cm<sup>-1</sup> : 1328 (w), 1447 (w), 1606 (m), 1622 (m), 2915 (m).

#### 10 Preparation 125

N-(3-{6-Methyl-3-[3-(2-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



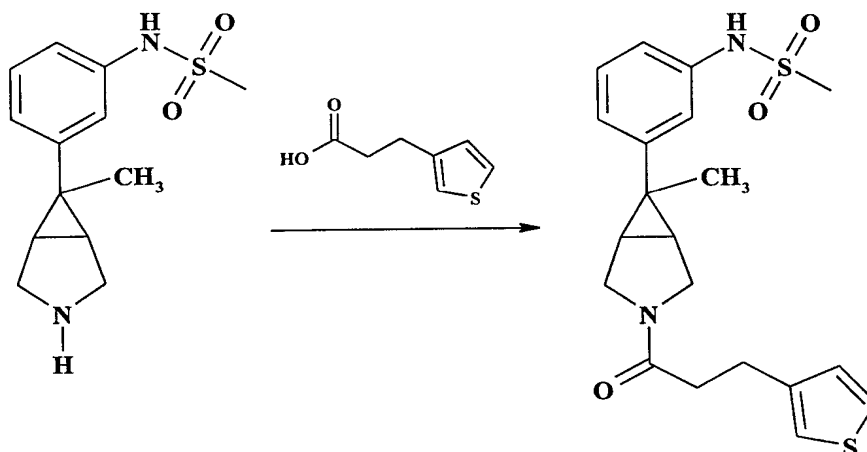
15

To a solution of 3-(2-thienyl)propanoic acid (200 mg, 1.2 mmol) in *N,N*-dimethylformamide (25 ml) was added 1-hydroxybenzotriazole monohydrate (200 mg, 1.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol). After stirring at room temperature for 10 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.3 mmol) and sodium hydrogen carbonate (220 mg, 2.6 mmol). The reaction

- mixture was stirred at room temperature for 3 h before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (1 x 30 ml and 2 x 15 ml). The combined organic extracts were washed with water (15 ml) and saturated brine (15 ml), dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to give a buff solid. The crude product was sonicated in methanol (5 ml) to afford the title compound as an off-white solid (350 mg, 66%, m.p. 184.5 °C). NMR (CDCl<sub>3</sub>, selected data) : 1.20 (s, 3H), 1.95 (m, 2H), 2.60 (m, 2H), 3.00 (s, 3H), 3.25 (m, 2H), 3.55 (d, 1H), 3.70-3.85 (m, 3H), 6.62 (br., 1H), 6.85 (m, 1H), 6.95 (m, 1H), 7.00-7.20 (m, 4H), 7.22-7.35 (m, 1H).
- MS (electrospray) : M/Z (MH<sup>+</sup>) 405.1; C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 405.1.

### Preparation 126

N-(3-{6-Methyl-3-[3-(3-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

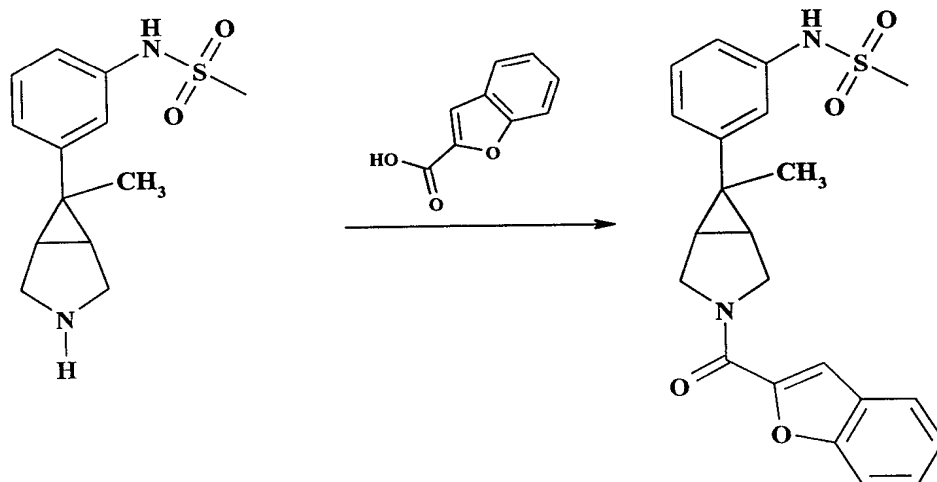


- To a solution of 3-(3-thienyl)propanoic acid (200 mg, 1.2 mmol) in *N,N*-dimethylformamide (25 ml) was added 1-hydroxybenzotriazole monohydrate (200 mg, 1.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol). After stirring at room temperature for 10 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-

azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.3 mmol) and sodium hydrogen carbonate (220 mg, 2.6 mmol). The reaction mixture was stirred at room temperature for 72 h before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (1 x 20 ml and 2 x 15 ml). The combined organic extracts were washed with water (15 ml) and saturated brine (15 ml), dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to give a buff solid. The crude product was sonicated in methanol (5 ml) to afford the title compound as an off-white solid (330 mg, 63%, m.p. 179.7 °C). NMR (CDCl<sub>3</sub>, selected data) : 1.20 (s, 3H), 1.95 (m, 2H), 2.55 (m, 2H), 2.90-3.10 (m, 5H), 3.50 (m, 1H), 3.60-3.80 (m, 3H), 6.60 (br., 1H), 6.95-7.15 (m, 5H), 7.20-7.30 (m, 2H). MS (electrospray) : M/Z (MH<sup>+</sup>) 405.1; C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 405.1.

#### Preparation 127

15 N-{3-[3-(1-Benzofuran-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



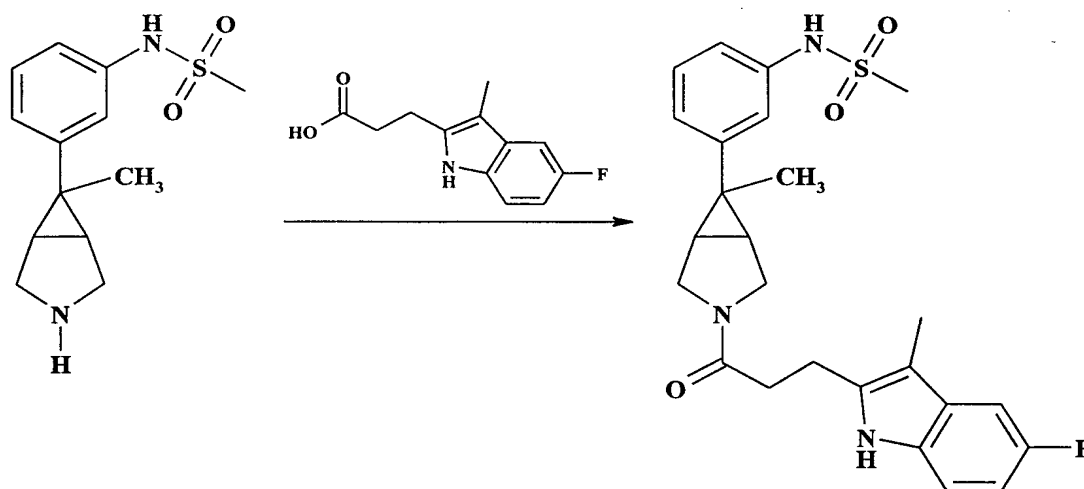
20 To a solution of 1-benzofuran-2-carboxylic acid (201 mg, 1.24 mmol) in *N,N*-dimethylformamide (25 ml) was added 1-hydroxybenzotriazole monohydrate (200

- mg, 1.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol). After stirring at room temperature for 10 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.3 mmol) and sodium hydrogen carbonate (220 mg, 2.6 mmol). The reaction mixture was stirred at room temperature overnight before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were treated with water (15 ml) upon which a buff solid precipitated. The biphasic mixture was filtered to afford 380 mg of a buff solid. The biphasic filtrate was separated and the organic layer was dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford a further 80 mg of buff solid. The combined buff solid was warmed to 60 °C in methanol and allowed to slowly cool to room temperature upon which the title compound was collected by filtration as an off-white solid (340 mg, 63%).
- NMR (DMSO, selected data) : 1.20 (s, 3H), 2.02 (m, 2H), 2.95 (s, 3H), 3.75-3.90 (m, 2H), 4.02 (m, 1H), 4.25 (m, 1H), 7.00-7.08 (m, 2H), 7.15 (s, 1H), 7.2-7.35 (m, 2H), 7.45 (dd, 1H), 7.55 (s, 1H), 7.68 (d, 1H), 7.78 (d, 1H).
- MS (electrospray) : M/Z (MH<sup>+</sup>) 411.1; C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S + H requires 411.1.

## 20 Preparation 128

*N*-(3-{3-[3-(5-Fluoro-3-methyl-1*H*-indol-2-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

265



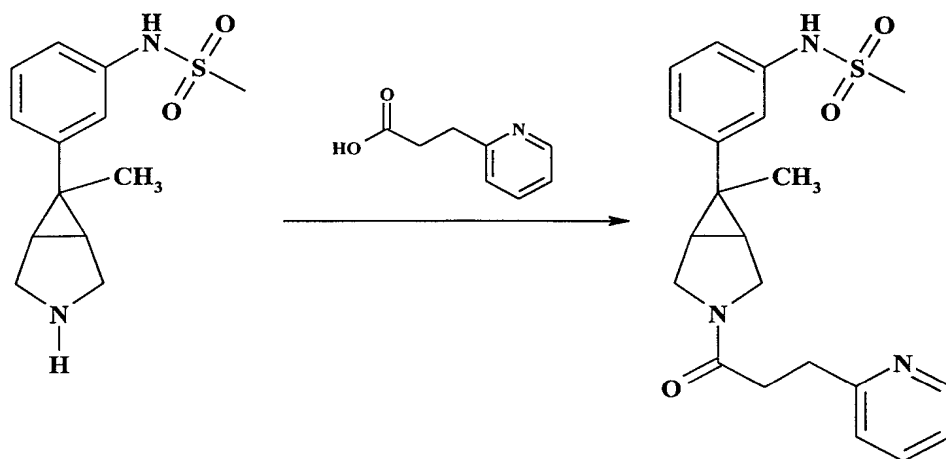
To a solution of 3-(5-fluoro-3-methyl-1*H*-indol-2-yl)propanoic acid (prepared according to the method described in EP 510398 A2, 200 mg, 0.90 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (154 mg, 1.00 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (262 mg, 1.36 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 308 mg, 0.90 mmol) and sodium hydrogen carbonate (150 mg, 1.80 mmol). The reaction mixture was stirred at room temperature overnight before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with water (15 ml), dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 350 mg of a brown viscous oil which was not purified further.

NMR (CDCl<sub>3</sub>, selected data) : 1.15 (s, 3H), 1.95 (m, 2H), 2.20 (s, 3H), 2.50 (m, 2H), 3.00 (s, 3H), 3.18 (m, 2H), 3.50 (m, 1H), 3.60-3.80 (m, 3H), 6.60 (br. s, 1H), 6.82 (dd, 1H), 7.00-7.15 (m, 4H), 7.18 (m, 1H), 7.25 (m, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 470.2; C<sub>25</sub>H<sub>28</sub>FN<sub>3</sub>O<sub>3</sub>S + H requires 470.2.

#### Preparation 129

*N*-(3-{6-Methyl-3-[3-(2-pyridinyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

To a solution of 3-(2-pyridinyl)propanoic acid (prepared according to the method described in WO 9730045 A1, 32 mg, 0.212 mmol) in *N,N*-dimethylformamide (2 ml) was added 1-hydroxybenzotriazole monohydrate (32 mg, 0.209 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (41 mg, 0.214 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 64 mg, 0.212 mmol) and sodium hydrogen carbonate (36 mg, 0.424 mmol). The reaction mixture was stirred at room temperature for 5 d. Water (5 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 70 mg of a brown oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with dichloromethane : ethanol : 0.880 ammonia (400 : 8 : 1 then 300 : 8 : 1) to afford the title compound as a colourless oil (17 mg, 20%).

NMR (CDCl<sub>3</sub>, selected data) : 1.18 (s, 3H), 1.95 (m, 2H), 2.75 (m, 2H), 3.00 (s, 3H), 3.20 (dd, 2H), 3.60 (m, 1H), 3.70 (m, 2H), 3.80 (dd, 1H), 7.00-7.18 (m, 4H), 7.20-7.30 (m, 2H), 7.45 (br. s, 1H), 7.58 (m, 1H), 8.50 (d, 1H).



MS (electrospray) : M/Z ( $M+H^+$ ) 400.2;  $C_{21}H_{25}N_3O_3S + H$  requires 400.2.

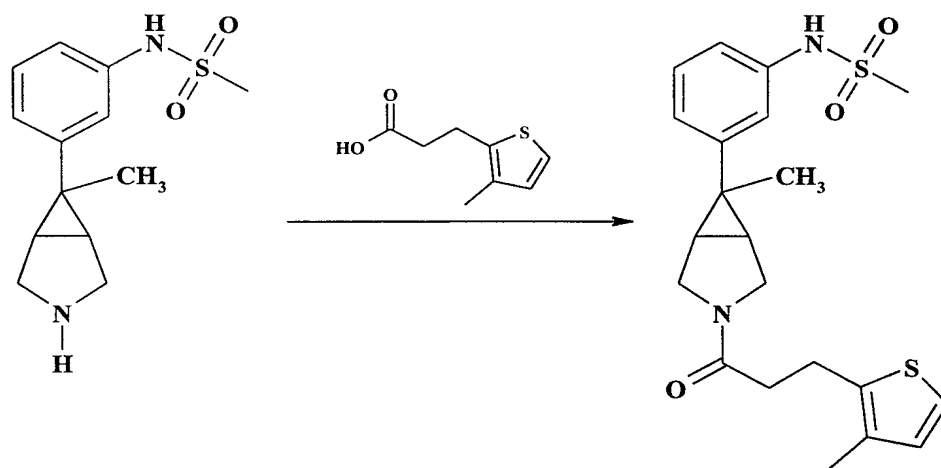
M/Z ( $MNa^+$ ) 422.2;  $C_{21}H_{25}N_3O_3S + Na$  requires 422.2.

IR  $\nu_{max}$  (polyethylene card)/ $cm^{-1}$  : 2360 (s), 2341 (m), 1624 (m), 1437 (w), 1238 (w), 1154 (w).

5

### Preparation 130

N-(3-{6-Methyl-3-[3-(3-methyl-2-thienyl)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



10

To a solution of 3-(3-methyl-2-thienyl)propanoic acid (J. W. McFarland et al., J. Med. Chem., 1970, 13, 113, 200 mg, 1.17 mmol) in *N,N*-dimethylformamide (25 ml) was added 1-hydroxybenzotriazole monohydrate (200 mg, 1.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.32 mmol) and sodium hydrogen carbonate (200 mg, 2.38 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. Water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (10 ml), dried ( $MgSO_4$ ), and

20

concentrated *in vacuo* to afford 620 mg of a brown oil. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100 over 30 min) and then with ethyl acetate : methanol (100 : 0 to 0 : 100 over 5 min) to afford the title compound as a colourless oil (244 mg, 50%).

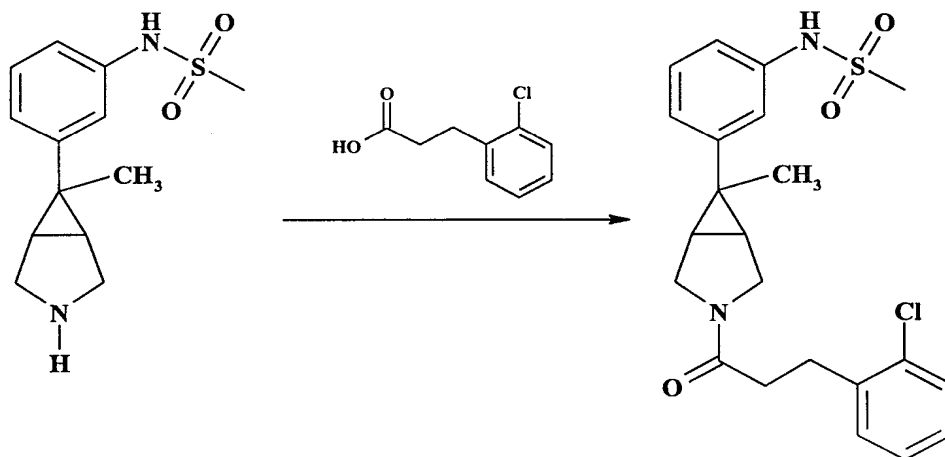
NMR (CDCl<sub>3</sub>, selected data) : 1.19 (s, 3H), 1.95 (m, 2H), 2.20 (s, 3H), 2.48 (m, 2H), 3.00 (s, 3H), 3.15 (dd, 2H), 3.55 (m, 1H), 3.70-3.80 (m, 1H), 6.65 (br. s 1H), 6.78 (d, 1H), 7.00-7.15 (m, 4H), 7.25 (m, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 419.1; C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 419.1.

M/Z (MNa<sup>+</sup>) 441.1; C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S + Na requires 441.1.

### Preparation 131

N-(3-{3-[3-(2-Chlorophenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of 3-(2-chlorophenyl)propanoic acid (200 mg, 1.08 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (187 mg, 1.22 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (318 mg, 1.66 mmol). After stirring at room temperature for 10

min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 400 mg, 1.32 mmol) and sodium hydrogen carbonate (200 mg, 2.38 mmol). The reaction mixture was stirred at room temperature for 3 d and then concentrated *in vacuo*.

5 Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with water (10 ml), dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 510 mg of a light brown oil. Sonication for 5 min at room temperature in dichloromethane (5 ml) followed by filtration afforded the title compound as an off-white solid (124 mg, 27%).

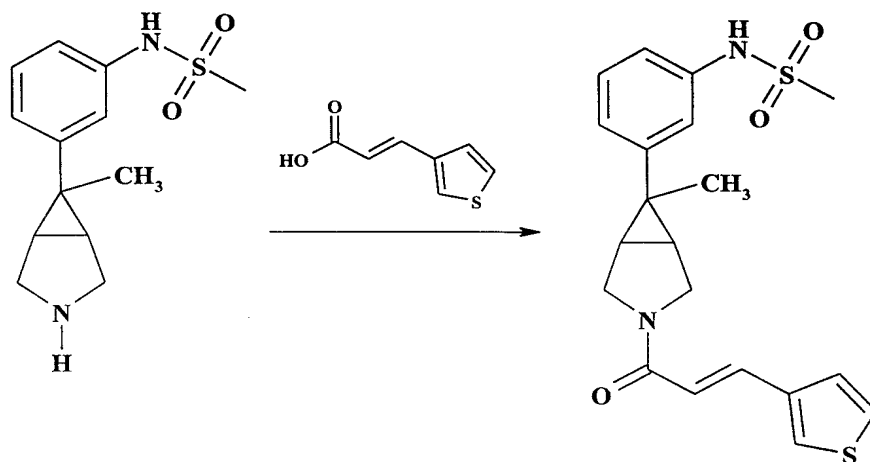
10 NMR (CDCl<sub>3</sub>, selected data) : 1.18 (s, 3H), 1.95 (m, 2H), 2.60 (t, 2H), 3.00 (s, 3H), 3.12 (dd, 2H), 3.55 (m, 1H), 3.70-3.80 (m, 3H), 6.55 (br. s 1H), 7.00-7.20 (m, 4H), 7.25-7.40 (m, 4H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 433.1; C<sub>22</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>S + H requires 433.1.

15

### Preparation 132

*N*-(3-{6-Methyl-3-[(*E*)-3-(3-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



To a solution of (*E*)-3-(3-thienyl)-2-propenoic acid (200 mg, 1.08 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (225 mg, 1.47 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (328 mg, 1.71 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 449 mg, 1.48 mmol) and sodium hydrogen carbonate (225 mg, 2.68 mmol). The reaction mixture was stirred at room temperature for 7 d and then concentrated *in vacuo*. Attempted partition between water (10 ml) and ethyl acetate (15 ml) produced a buff solid which was collected by filtration. Sonication for 5 min at room temperature in dichloromethane (5 ml) followed by filtration afforded the title compound as an off-white solid (430 mg, 72%).

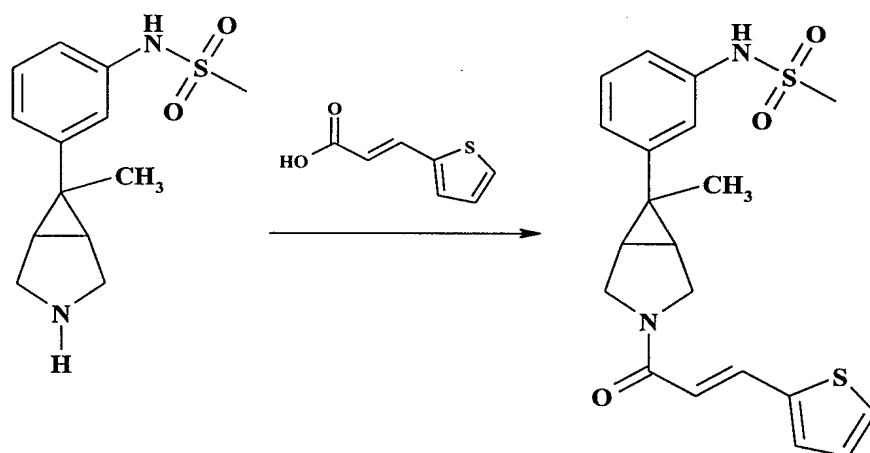
NMR (DMSO, selected data) : 1.18 (s, 3H), 1.95 (ddd, 2H), 2.95 (s, 3H), 3.58 (d, 1H), 3.68 (dd, 1H), 3.82 (d, 1H), 3.95 (dd, 1H), 6.78 (d, 1H), 6.98-7.05 (m, 2H), 7.10 (s, 1H), 7.22 (dd, 1H), 7.45 (d, 1H), 7.52-7.60 (m, 2H), 7.83 (m, 1H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 403.1; C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 403.1.

#### Preparation 133

*N*-(3-{6-Methyl-3-[(*E*)-3-(2-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

271



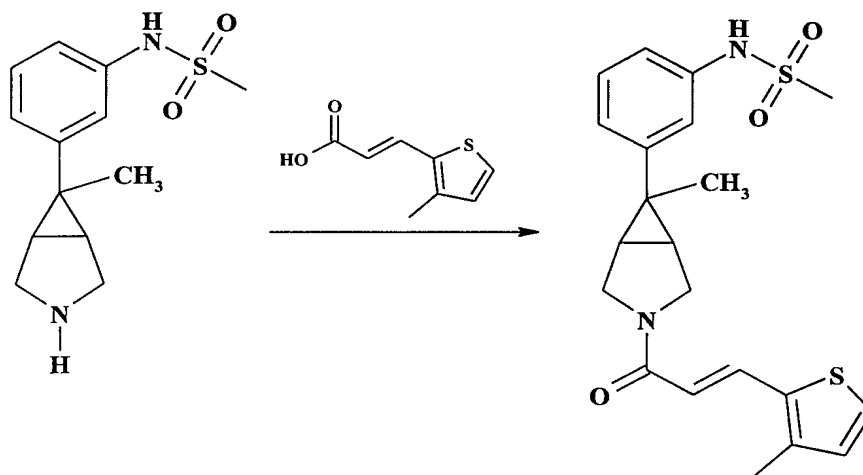
To a solution of (*E*)-3-(2-thienyl)-2-propenoic acid (200 mg, 1.08 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (225 mg, 1.47 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (328 mg, 1.71 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 449 mg, 1.48 mmol) and sodium hydrogen carbonate (225 mg, 2.68 mmol). The reaction mixture was stirred at room temperature for 7 d and then concentrated *in vacuo*. Attempted partition between water (15 ml) and ethyl acetate (20 ml) produced a buff solid which was collected by filtration. Sonication for 5 min at room temperature in dichloromethane (5 ml) followed by filtration afforded the title compound as an off-white solid (337 mg, 77%).

NMR (DMSO, selected data) : 1.18 (s, 3H), 1.95 (ddd, 2H), 2.95 (s, 3H), 3.58 (d, 1H), 3.68 (dd, 1H), 3.80 (d, 1H), 3.95 (dd, 1H), 6.60 (d, 1H), 6.95-7.05 (m, 2H), 7.10-7.15 (m, 2H), 7.22 (dd, 1H), 7.43 (d, 1H), 7.58-7.65 (m, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 403.0; C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 403.1.

## Preparation 134

*N*-(3-{6-Methyl-3-[(*E*)-3-(3-methyl-2-thienyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

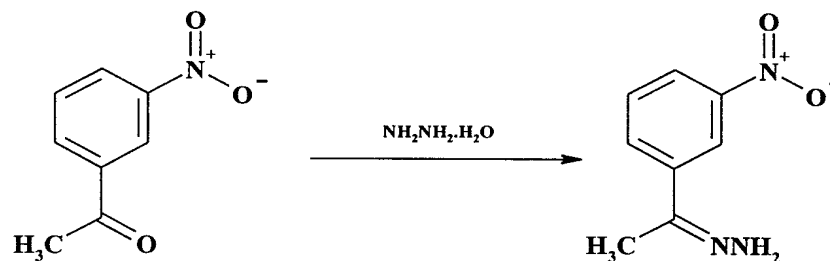


To a solution of (*E*)-3-(3-methyl-2-thienyl)-2-propenoic acid (200 mg, 1.00 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (212 mg, 1.39 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (352 mg, 1.84 mmol). After stirring at room temperature for 10 min, the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 414 mg, 1.36 mmol) and sodium hydrogen carbonate (225 mg, 2.68 mmol). The reaction mixture was stirred at room temperature for 7 d and then concentrated *in vacuo*. Attempted partition between water (15 ml) and ethyl acetate (20 ml) produced a buff solid which was collected by filtration. Sonication for 5 min at room temperature in dichloromethane (5 ml) followed by filtration afforded the title compound as an off-white solid (280 mg, 67%).

NMR (DMSO, selected data) : 1.18 (s, 3H), 1.95 (ddd, 2H), 2.28 (s, 3H), 2.95 (s, 3H), 3.59 (d, 1H), 3.70 (dd, 1H), 3.80 (d, 1H), 3.97 (dd, 1H), 6.47 (d, 1H), 6.95 (d, 1H), 6.97-7.03 (m, 2H), 7.10 (s, 2H), 7.22 (dd, 1H), 7.43 (d, 1H), 7.58-7.65 (m, 2H).

MS (thermospray) : M/Z (MH<sup>+</sup>) 417.1; C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> + H requires 417.1.

#### Preparation 135

1-(3-Nitrophenyl)-1-ethanone hydrazone

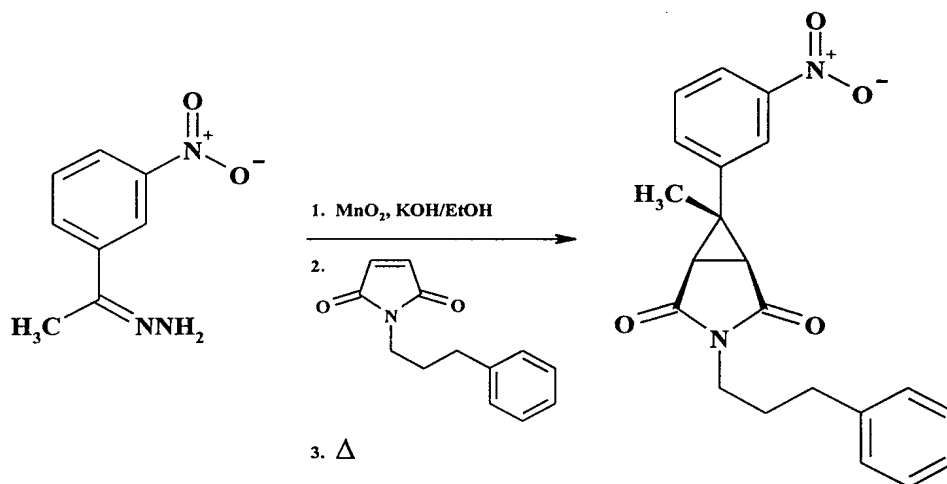
- 5 To a solution of 3-nitroacetophenone (200 g, 1.12 mol) in Industrial Methylated Spirits (1.2 l) was added hydrazine monohydrate (140 ml, 2.25 mol) and the reaction mixture was heated under reflux for 2h. Water (1.2 l) was added and the reaction mixture was cooled to room temperature. The resulting precipitate was collected by filtration to afford the title compound as a yellow crystalline solid
- 10 (180 g, 82%).

NMR (CDCl<sub>3</sub>, selected data) : 2.15 (s, 3H), 5.52 (br. s, 2H), 7.48 (dd, 1H), 7.99 (d, 1H), 8.12 (d, 1H), 8.46 (s, 1H).

MS (APCI) : m/z (MH<sup>+</sup>) 180.5; C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub> + H requires 180.1.

15 Preparation 136

6-Methyl-6-(2-nitrophenyl)-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane-2,4-dione



To a solution of 1-(3-nitrophenyl)-1-ethanone hydrazone (Preparation 135, 100 g, 0.56 mol) in dioxan (1 l) was added manganese (IV) oxide (200 g, 2.3 mol) and the reaction mixture was stirred at room temperature for 30 min. The suspension was filtered through Celite<sup>TM</sup> washing with dioxan (*ca.* 200 ml). 1-(3-Phenylpropyl)-1*H*-pyrrole-2,4-dione (Preparation 80, 110 g, 0.54 mol) was added to the filtrate and the reaction mixture was stirred at room temperature for 4 h before heating under reflux for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was triturated in methanol (500 ml) and the precipitate was collected by filtration to afford the title compound as a white crystalline solid (121 g, 65%).

NMR ( $\text{CDCl}_3$ , selected data) : 1.51 (m, 3H), 1.93 (m, 2H), 2.65 (t, 2H), 2.77 (s, 2H), 3.50 (t, 2H), 7.15-7.19 (m, 3H), 7.24-7.30 (m, 2H), 7.54 (dd, 1H), 7.65 (d, 1H), 8.15 (d, 1H), 8.19 (s, 1H).

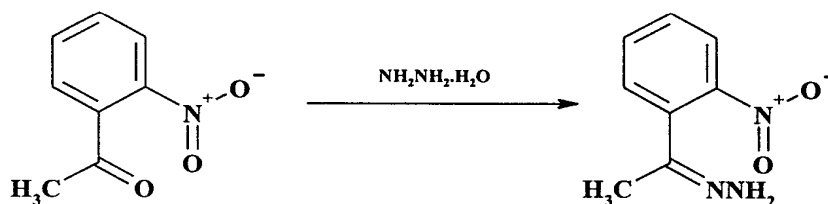
MS (APCI) :  $m/z$  ( $\text{MH}^+$ ) 365.5;  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4 + \text{H}$  requires 365.2.

### Preparation 137

#### 1-(2-Nitrophenyl)-1-ethanone hydrazone



275

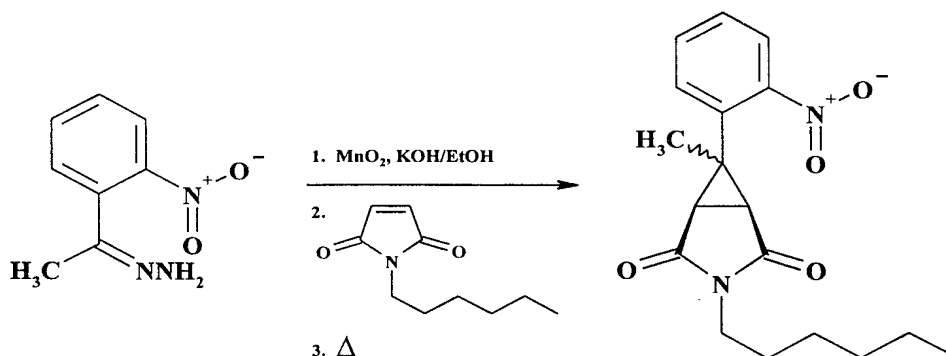


To a solution of 2'-nitroacetophenone (8.26 g, 50.00 mmol) in ethanol (50 ml) was added hydrazine monohydrate (4.85 ml, 100 mmol) and the reaction mixture was heated at 70 °C for 5 h. The reaction mixture was cooled to room temperature and water (100 ml) was added. After 5 d, the reaction mixture was concentrated *in vacuo* to *ca.* 100 ml and diethyl ether (100 ml) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (100 ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to afford *ca.* 8.0 g of a crude yellow oil. This was purified by chromatography in two batches using a Biotage Flash 40M<sup>TM</sup> cartridge packed with silica gel (90 g) eluting with dichloromethane : diethyl ether (19 : 1) to afford the title compound as viscous yellow oil (4.20 g, 45%).

NMR (CDCl<sub>3</sub>, selected data) : 2.05 (s, 3H), 5.40 (br. s, 2H), 7.42-7.50 (m, 2H), 7.60 (dd, 1H), 7.90 (d, 1H).

### Preparation 138

#### 3-Hexyl-6-methyl-6-(2-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione



To a solution of 1-(2-nitrophenyl)-1-ethanone hydrazone (Preparation 137, 4.00 g, 22.3 mmol) in dioxan (50 ml) was added manganese (IV) oxide (4.27 g, 49.2 mmol) followed by a saturated ethanolic solution of potassium hydroxide (2.0 ml), and the reaction mixture was stirred at room temperature for 4 h. The suspension was filtered through Celite™ washing with dioxan (*ca.* 150 ml) to give a deep red solution. 1-Hexyl-1*H*-pyrrole-2,4-dione (Preparation 56, 4.05 g, 22.4 mmol) was added to the solution and the reaction mixture was stirred at room temperature overnight before heating under reflux for 24 h. The reaction mixture was cooled to room temperature, filtered through Celite™ and concentrated *in vacuo* a crude dark brown oil. This was purified by chromatography in two batches using a Biotage Flash 40M™ cartridge packed with silica gel (90 g) eluting with dichloromethane : hexane (2 : 1) to afford an 8 : 1 *exo* : *endo* mixture of diastereomers of the title compound as a pale brown oil (880 mg, 12%).

NMR (CDCl<sub>3</sub>, selected data for the *exo* isomer) : 0.90 (m, 3H), 1.25-1.40 (m, 6H), 1.55-1.60 (m, 5H), 2.62 (s, 2H), 3.42 (m, 2H), 7.45 (m, 1H), 7.60-7.65 (m, 2H), 7.95 (d, 1H).

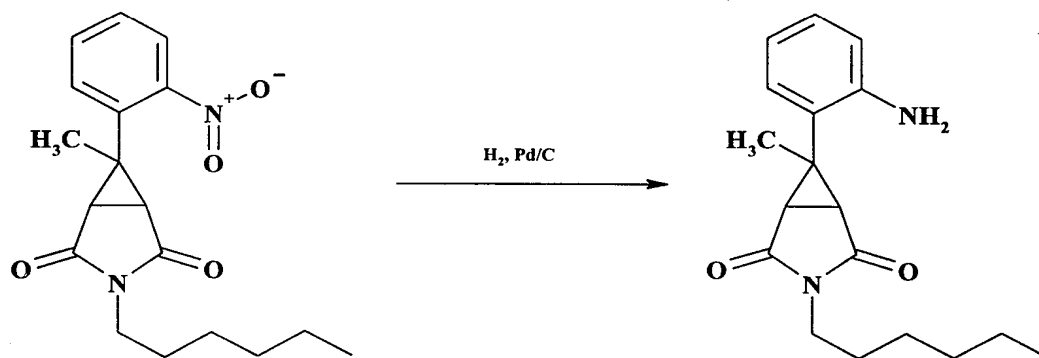
NMR (CDCl<sub>3</sub>, selected data for the *endo* isomer) : 0.82 (m, 3H), 1.20-1.30 (m, 6H), 1.45 (m, 2H), 2.22 (s, 3H), 3.30-3.48 (m, 4H), 7.20 (d, 1H), 7.52 (dd, 1H), 7.62 (dd, 1H), 8.18 (d, 1H).

MS (electrospray) : *m/z* (MH<sup>+</sup>) 331.2; C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> + H requires 331.2.

*m/z* (MNa<sup>+</sup>) 353.1; C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> + Na requires 353.1.

#### Preparation 139

6-(2-Aminophenyl)-3-hexyl-6-methylazabicyclo[3.1.0]hexane-2,4-dione



To a solution of 3-hexyl-6-methyl-6-(2-nitrophenyl)azabicyclo[3.1.0]hexane-2,4-dione (Preparation 138, 880 mg, 2.66 mmol) in tetrahydrofuran (10 ml) was added 5% palladium on charcoal (Johnson Matthey type 87, 50 mg) and the reaction mixture was placed under an atmosphere of hydrogen (60 psi) at room temperature for 4 h. The catalyst was removed by filtration through Celite™ and the filtrate was concentrated *in vacuo*. The residue was flushed through a small plug of silica gel (<1 g) eluting with dichloromethane to afford only the exo isomer of the title compound as a pale yellow oil (310 mg, 39 %).

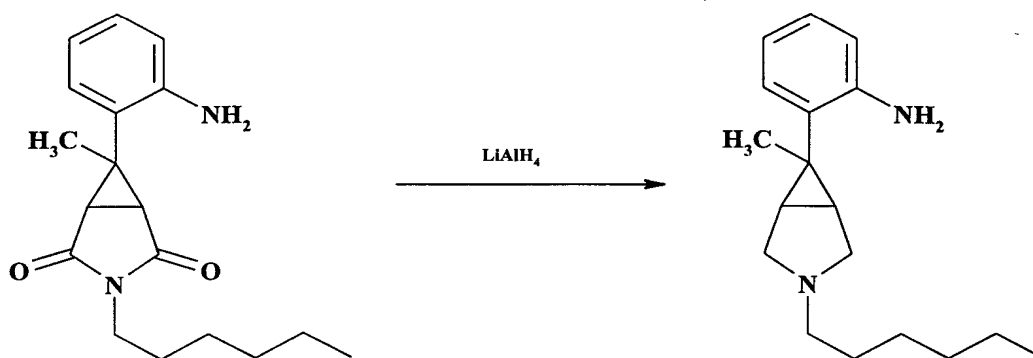
NMR (CDCl<sub>3</sub>, selected data) : 0.90 (m, 3H), 1.15-1.40 (m, 6H), 1.45 (m, 2H), 1.60 (s, 3H), 2.75 (m, 2H), 3.45 (m, 2H), 3.90 (br. s 2H), 6.65-6.80 (m, 2H), 7.08-7.18 (m, 2H).

MS (thermospray) : m/z (MH<sup>+</sup>) 301.1; C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> + H requires 301.2.

#### Preparation 140

#### 2-[3-Hexyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenylamine

278



To a solution of 6-(2-aminophenyl)-3-hexyl-6-methylazabicyclo[3.1.0]hexane-2,4-dione (Preparation 139, 310 mg, 1.03 mmol) in tetrahydrofuran (10 ml) under nitrogen at 0 °C was added dropwise a 1.0M solution of lithium aluminium hydride in tetrahydrofuran (2.5 ml, 2.5 mmol), and the reaction mixture was allowed to stir at room temperature for 4 h. The rapidly stirred reaction mixture was treated sequentially with water (2.5 ml), sodium carbonate (2.5 g) and ethyl acetate (25 ml). The reaction mixture was stirred for 1 h, filtered and concentrated *in vacuo*. This was purified by chromatography using a Biotage Flash 12<sup>TM</sup> cartridge packed with silica gel (8 g) eluting with ethyl acetate : hexane : 0.880 ammonia (25 : 75 : 1) to afford the title compound as a pale yellow oil (123 mg, 44%).

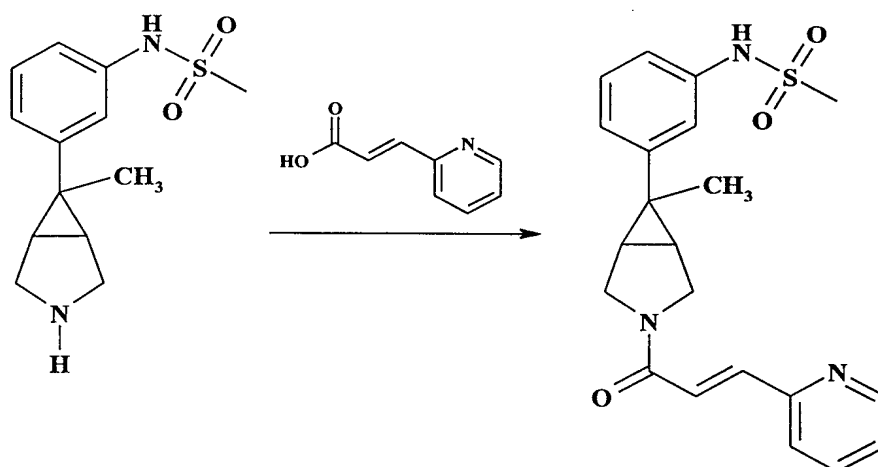
NMR (CDCl<sub>3</sub>, selected data) : 0.90 (m, 3H), 1.15-1.40 (m, 6H), 1.45 (m, 2H), 1.60 (s, 3H), 2.75 (m, 2H), 3.45 (m, 2H), 3.90 (br. s 2H), 6.65-6.80 (m, 2H), 7.08-7.18 (m, 2H).

MS (electrospray) : m/z (MH<sup>+</sup>) 267.2; C<sub>18</sub>H<sub>22</sub>N<sub>2</sub> + H requires 267.2.

#### Preparation 141

*N*-(3-{6-Methyl-3-[(*E*)-3-(2-pyridinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

279



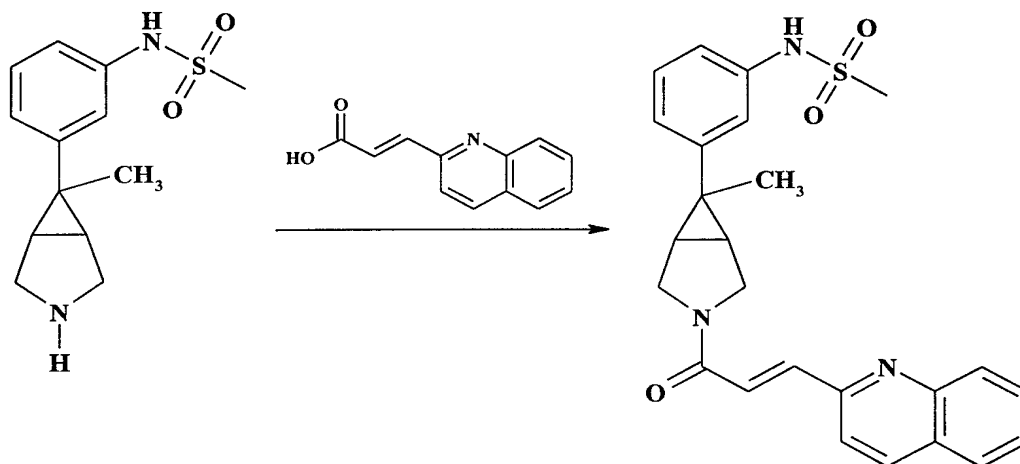
A solution of 1-hydroxybenzotriazole monohydrate (224 mg, 1.46 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (306 mg, 1.60 mmol) in *N,N*-dimethylformamide (10 ml) was added to (*E*)-3-(2-pyridinyl)-2-propenoic acid (197 mg, 1.32 mmol). After stirring at room temperature for 15 min, the mixture was added to the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 404 mg, 1.32 mmol) and sodium hydrogen carbonate (220 mg, 2.64 mmol). The reaction mixture was stirred at room temperature for overnight and then water (20 ml) and dichloromethane (10 ml) were added. The biphasic mixture was separated by filtering through a Whatman Microfiltration Device Filter Tube, and the resulting organic extract was concentrated using a stream of nitrogen to afford 377 mg of a crude dark brown oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (100 : 2 : 1) to afford the title compound as a white solid (172 mg, 33%).

NMR (CDCl<sub>3</sub>, selected data) : 1.25 (s, 3H), 2.02 (m, 2H), 3.00 (s, 3H), 3.80-3.95 (m, 3H), 4.05 (dd, 1H), 7.05-7.18 (m, 2H), 7.20-7.30 (m, 3H), 7.35 (d, 1H), 7.41 (d, 1H), 7.72 (dd, 1H), 7.79 (d, 1H), 8.62 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 398; C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 398.

Preparation 142

*N*-(3-{6-Methyl-3-[(*E*)-3-(2-quinolinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



5

A solution of 1-hydroxybenzotriazole monohydrate (112 mg, 0.73 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) in *N,N*-dimethylformamide (5 ml) was added to (*E*)-3-(2-quinolinyl)-2-propenoic acid (M. Hamana, K. Funakoshi and Y. Kuchino, Chem. Pharm. Bull., 1974, 22, 1806; 131 mg, 0.66 mmol). After stirring at room temperature for 15 min, the mixture was added to the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 202 mg, 0.66 mmol) and sodium hydrogen carbonate (110 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for overnight and then water (10 ml) and dichloromethane (5 ml) were added. The biphasic mixture was separated by filtering through a Whatman Microfiltration Device Filter Tube, and the resulting organic extract was concentrated using a stream of nitrogen to afford 400 mg of a crude dark red oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (100 : 2 : 1) to afford the title compound as a cream solid (206 mg, 70%).

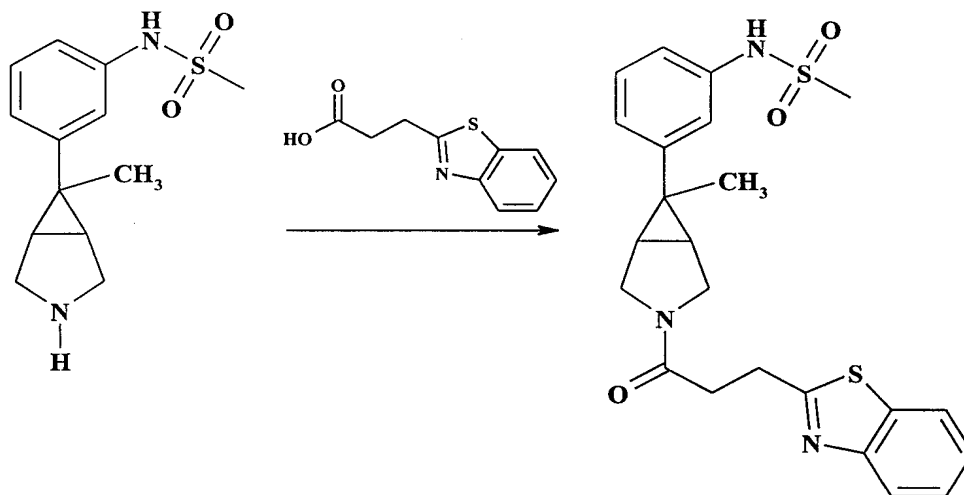
NMR (CDCl<sub>3</sub>, selected data) : 1.32 (s, 3H), 2.05 (m, 2H), 3.02 (s, 3H), 3.85-3.95 (m, 2H), 4.00 (d, 1H), 4.15 (dd, 1H), 6.88 (br. s, 1H), 7.15 (dd, 1H), 7.20-7.35 (m, 2H), 7.48 (d, 1H), 7.52-7.60 (m, 2H), 7.75 (dd, 1H), 7.82 (d, 1H), 7.95 (d, 1H), 8.12 (d, 1H), 8.19 (d, 1H).

5 MS (electrospray) : M/Z (MH<sup>+</sup>) 448; C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 448.

### Preparation 143

N-(3-{3-[3-(1,3-Benzothiazol-2-yl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide

10



A solution of 1-hydroxybenzotriazole monohydrate (112 mg, 0.73 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) in *N,N*-dimethylformamide (5 ml) was added to 3-(1,3-benzothiazol-2-yl)propanoic acid (P. Baudet and C. Otten, *Helv. Chim. Acta*, 1970, 53, 1683; 137 mg, 0.66 mmol). After stirring at room temperature for 15 min, the mixture was added to the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 202 mg, 0.66 mmol) and sodium hydrogen carbonate (110 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for overnight and then water (10 ml) and dichloromethane (5

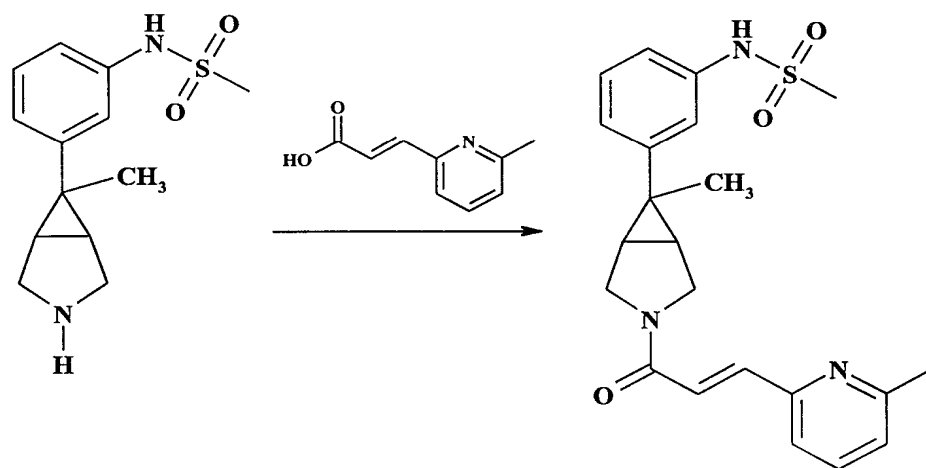
ml) were added. The biphasic mixture was separated by filtering through a Whatman Microfiltration Device Filter Tube, and the resulting organic extract was concentrated using a stream of nitrogen to afford 326 mg of a crude dark green solid. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (100 : 2 : 1) to afford the title compound as an off-white solid (228 mg, 76%).

NMR (CDCl<sub>3</sub>, selected data) : 1.30 (s, 3H), 2.02 (m, 2H), 3.00 (s, 3H), 3.78-3.90 (m, 3H), 4.00 (dd, 1H), 6.47 (br. s, 1H), 6.63 (d, 1H), 7.03-7.15 (m, 3H), 7.29 (dd, 1H), 7.46 (dd, 1H), 7.56 (dd, 1H), 7.67-7.73 (m, 2H), 8.06 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 456; C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> + H requires 456.

#### Preparation 144

N-(3-{6-Methyl-3-[(E)-3-(6-methyl-2-pyridinyl)-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



A solution of 1-hydroxybenzotriazole monohydrate (112 mg, 0.73 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) in *N,N*-dimethylformamide (5 ml) was added to (E)-3-(6-methyl-2-pyridinyl)-2-propenoic acid (F. Freeman, L. Y. Chang, J. C. Kappos and L. Sumarta, J. Org.



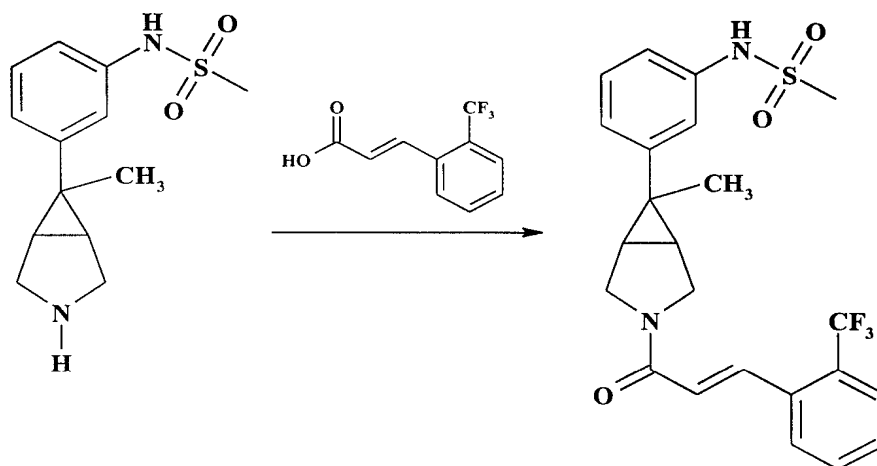
Chem., 1987, 52, 1460; 108 mg, 0.66 mmol). After stirring at room temperature for 15 min, the mixture was added to the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 202 mg, 0.66 mmol) and sodium hydrogen carbonate (110 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for overnight and then water (10 ml) and dichloromethane (5 ml) were added. The biphasic mixture was separated by filtering through a Whatman Microfiltration Device Filter Tube, and the resulting organic extract was concentrated using a stream of nitrogen to afford 290 mg of a crude cream solid. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (100 : 2 : 1) to afford the title compound as a white solid (191 mg, 70%).

NMR (CDCl<sub>3</sub>, selected data) : 1.27 (s, 3H), 2.02 (m, 2H), 2.60 (s, 3H), 3.01 (s, 3H), 3.82-3.98 (m, 3H), 4.08 (dd, 1H), 6.87 (br. s, 1H), 7.07-7.15 (m, 2H), 7.19-7.37 (m, 5H), 7.59 (dd, 1H), 7.73 (d, 1H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 412; C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S + H requires 412.

#### Preparation 145

*N*-(3-{6-Methyl-3-[(*E*)-3-(2-trifluoromethyl)phenyl]-2-propenoyl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl)methanesulfonamide



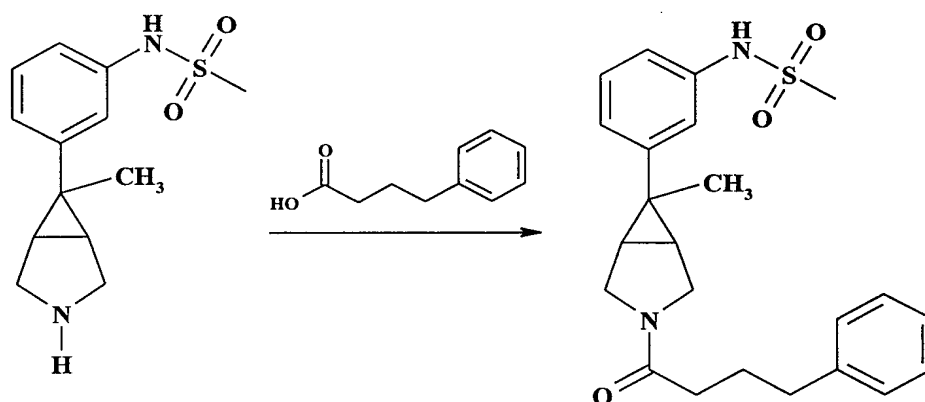
A solution of 1-hydroxybenzotriazole monohydrate (112 mg, 0.73 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) in *N,N*-dimethylformamide (5 ml) was added to (*E*)-3-(2-(trifluoromethyl)phenyl)-2-propenoic acid (143 mg, 0.66 mmol). After stirring at room temperature for 15 min, the mixture was added to the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 202 mg, 0.66 mmol) and sodium hydrogen carbonate (110 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for overnight and then water (10 ml) and dichloromethane (5 ml) were added. The biphasic mixture was separated by filtering through a Whatman Microfiltration Device Filter Tube, and the resulting organic extract was concentrated using a stream of nitrogen to afford 364 mg of a crude brown oil. This was purified by chromatography using a Biotage Flash 40S<sup>TM</sup> cartridge packed with silica gel (40 g) eluting with dichloromethane : ethanol : 0.880 ammonia (100 : 2 : 1) to afford the title compound as a yellow oil (240 mg, 78%).

NMR (CDCl<sub>3</sub>, selected data) : 1.30 (s, 3H), 2.02 (m, 2H), 3.00 (s, 3H), 3.78-3.90 (m, 3H), 4.00 (dd, 1H), 6.47 (br. s, 1H), 6.63 (d, 1H), 7.03-7.15 (m, 3H), 7.29 (dd, 1H), 7.46 (dd, 1H), 7.56 (dd, 1H), 7.67-7.73 (m, 2H), 8.06 (d, 1H).  
MS (electrospray) : M/Z (MH<sup>+</sup>) 465; C<sub>23</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 465.

#### Preparation 146

*N*-{3-[6-Methyl-3-(4-phenylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide

285



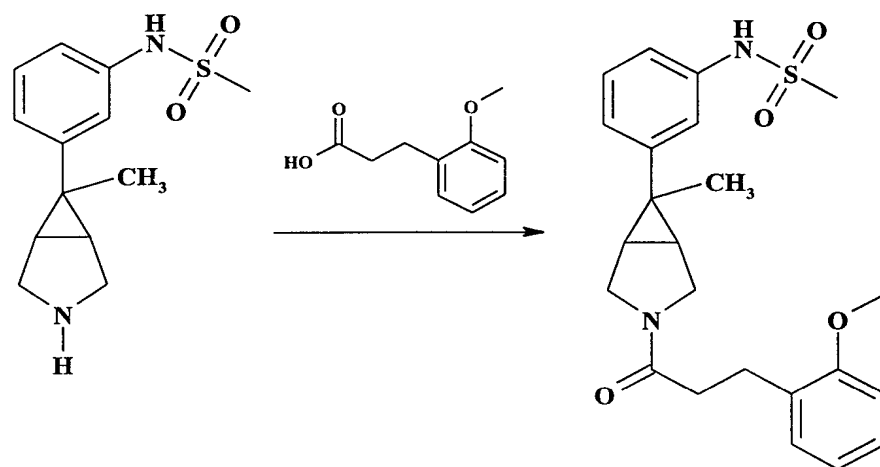
To a solution of 4-phenylbutanoic acid (219 mg, 1.33 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (225 mg, 1.48 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (382 mg, 1.98 mmol). After stirring at room temperature for 15 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 449 mg, 1.48 mmol) and sodium hydrogen carbonate (225 mg, 2.7 mmol). The reaction mixture was stirred at room temperature for overnight before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (20, 15 ml). The combined organic extracts were washed with water (15 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a colourless oil (540 mg). This was purified by chromatography using a Biotage Flash 12™ cartridge packed with silica gel (8 g) eluting with hexane : ethyl acetate (100 : 0 to 0 : 100 over 30 min) and then with ethyl acetate : methanol (100 : 0 to 0 : 100 over 5 min) to afford the title compound as a colourless glass (360 mg, 59%).

NMR (CDCl<sub>3</sub>, selected data) : 1.25 (s, 3H), 1.90-2.10 (m, 4H), 2.25 (t, 2H), 2.70 (t, 2H), 3.00 (s, 3H), 3.50 (d, 1H), 3.65-3.80 (m, 3H), 6.70 (br. s, 1H), 7.00-7.40 (m, 9H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 413; C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S + H requires 413.

Preparation 147

*N*-[3-{3-[3-(2-Methoxyphenyl)propanoyl]-6-methyl-3-azabicyclo[3.1.0]hex-6-yl}phenyl]methanesulfonamide



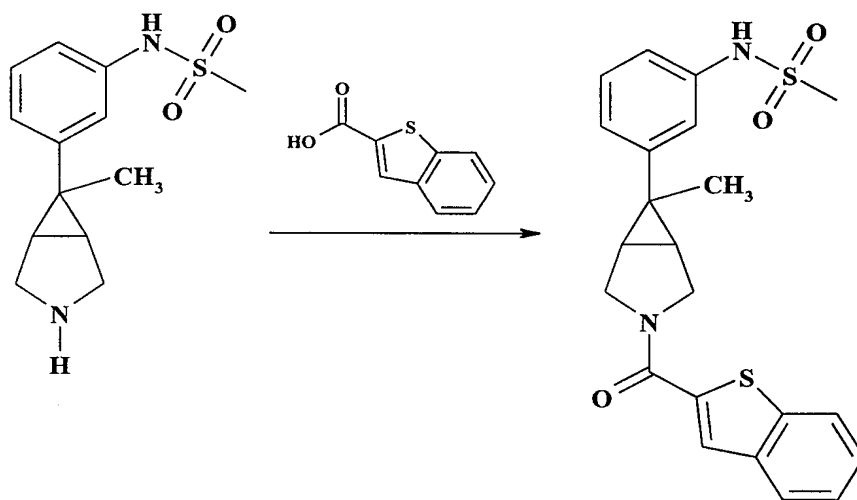
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- To a solution of 3-(2-methoxyphenyl)propanoic acid (240 mg, 1.33 mmol) in *N,N*-dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (225 mg, 1.48 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (382 mg, 1.98 mmol). After stirring at room temperature for 15 min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 449 mg, 1.48 mmol) and sodium hydrogen carbonate (225 mg, 2.7 mmol). The reaction mixture was stirred at room temperature for overnight before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with ethyl acetate (20, 15 ml). The combined organic extracts were washed with water (15 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a dark buff solid (470 mg). The crude product was sonicated in dichloromethane (5 ml) and collected by filtration to afford the title compound as an off-white solid (220 mg, 39%).
- NMR (CDCl<sub>3</sub>, selected data) : 1.18 (s, 3H), 1.93 (m, 2H), 2.58 (dd, 2H), 2.95-3.02 (m, 5H), 3.52 (d, 1H), 3.65-3.77 (m, 3H), 3.85 (s, 3H), 6.58 (br. s, 1H), 6.80-6.92 (m, 2H), 7.00-7.30 (m, 6H).

MS (electrospray) : M/Z (MH<sup>+</sup>) 429; C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S + H requires 429.

### Preparation 148

N-{3-[3-(1-Benzothiophen-2-ylcarbonyl)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl}methanesulfonamide



To a solution of 1-benzothiophene-2-carboxylic acid (236 mg, 1.33 mmol) in *N,N*-  
10 dimethylformamide (20 ml) was added 1-hydroxybenzotriazole monohydrate (225  
mg, 1.48 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
hydrochloride (382 mg, 1.98 mmol). After stirring at room temperature for 15  
min the mixture was treated with the hydrochloride salt of *N*-[3-(6-methyl-3-  
azabicyclo[3.1.0]hex-6-yl)phenyl]methanesulfonamide (Preparation 53, 449 mg,  
15 1.48 mmol) and sodium hydrogen carbonate (225 mg, 2.7 mmol). The reaction  
mixture was stirred at room temperature for overnight before concentrating *in vacuo*. Water (15 ml) was added and the reaction mixture was extracted with  
ethyl acetate (20, 15 ml). The combined organic extracts were washed with water  
(15 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give a buff solid  
20 (545 mg). The crude product was sonicated in dichloromethane (5 ml) and

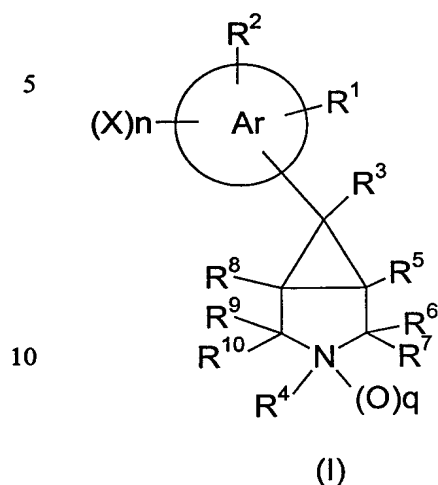
collected by filtration to afford the title compound as an off-white solid (410 mg, 72%).

NMR (DMSO, selected data) : 1.20 (s, 3H), 2.03 (m, 2H), 3.00 (m, 3H), 3.80-4.00 (m, 3H), 4.25 (m, 1H), 7.00-7.08 (m, 2H), 7.12 (s, 1H), 7.24 (dd, 1H),  
5 7.40-7.50 (m, 2H), 7.93-8.03 (m, 3H).

MS (electrospray) : M/Z ( $MH^+$ ) 427;  $C_{22}H_{22}N_2O_3S_2 + H$  requires 427.

CLAIMS

1. A substance which is a compound of formula I,



wherein the "Ar" ring represents an optionally benzo-fused phenyl or 5- or 6-  
15 membered heteroaryl ring;

R<sup>1</sup> when taken alone is H, halogen, NO<sub>2</sub>, NH<sub>2</sub>, NY<sup>2</sup>WY<sup>1</sup>, Het<sup>1</sup>, AD, CO<sub>2</sub>R<sup>7</sup>, C(O)R<sup>8</sup>,  
C(=NOH)R<sup>8</sup>, or OE,

20 Y<sup>2</sup> is H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> alkenyl (each of which alkyl and alkenyl is optionally  
substituted by aryl, aryloxy or Het<sup>1</sup>),

W is SO<sub>2</sub>, CO, C(O)O, P(Y<sup>1</sup>)=O, P(Y<sup>1</sup>)=S,

25 Y<sup>1</sup> is C<sub>1-10</sub> alkyl (optionally substituted by one or more substituents independently  
selected from halogen, OH, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkanoyloxy, CONH<sub>2</sub>, C<sub>1-6</sub>  
alkoxycarbonyl, NH<sub>2</sub>, aryl, mono- or di(C<sub>1-4</sub> alkyl)amino, C<sub>3-8</sub> cycloalkyl,  
phthalimidyl, Het<sup>1</sup>), Het<sup>1</sup>, aryl (optionally substituted by one or more substituents  
independently selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl and halogen), NH<sub>2</sub>, N(C<sub>1-6</sub> alkyl)<sub>2</sub>  
30 or NH(C<sub>1-6</sub> alkyl),

Het<sup>1</sup> is a heterocyclic group containing up to 4 heteroatoms selected from N, O and S, which may comprise up to 3 rings (preferably a heteroaryl group, optionally benzo- or pyrido-fused heteroaryl), optionally substituted by one or more substituents independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkoxy, C<sub>1-6</sub> haloalkyl, C<sub>3-6</sub> halocycloalkyl, =O, OH, halogen, NO<sub>2</sub>, SiR<sup>19a</sup>R<sup>19b</sup>R<sup>19c</sup>, CON<sup>20a</sup>R<sup>20b</sup>, NR<sup>20a</sup>R<sup>20b</sup>, SR<sup>21a</sup>, NR<sup>21b</sup>SO<sub>2</sub>R<sup>22a</sup>, NR<sup>21c</sup>C(O)OR<sup>22b</sup>, NR<sup>21d</sup>COR<sup>22d</sup>, and C<sub>1-6</sub> alkoxycarbonyl, and if a S atom is present in a ring, it can be present as part of a -S-, S(O)- or -S(O<sub>2</sub>)- group, and carbon atoms in the ring can be present as a part of a carbonyl moiety;

10

R<sup>19a</sup>, R<sup>19b</sup>, R<sup>19c</sup> each independently represent C<sub>1-6</sub> alkyl or aryl,

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R<sup>20a</sup> and R<sup>20b</sup> each independently represent H, C<sub>1-6</sub> alkyl, aryl, (C<sub>1-4</sub> alkyl)phenyl, each of which alkyl, aryl and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen, or R<sup>20a</sup> and R<sup>20b</sup> can be taken together with the N atom to which they are attached, to form a 4- to 6-membered ring optionally substituted by one or more substituents independently selected from one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, =O, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen,

20

R<sup>21a, b, c and d</sup> each independently represent H, C<sub>1-6</sub> alkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which alkyl, aryl, and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, halogen, NH<sub>2</sub>,

25

R<sup>22a, b and c</sup> each independently represent C<sub>1-6</sub> alkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which alkyl, aryl, and alkylphenyl are optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, OH, NO<sub>2</sub>, halogen, NH<sub>2</sub>,

30

A is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene or C<sub>2-4</sub> alkynylene, each of which is optionally substituted by one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogen and/or OH,

D is H, OH, CN, NR<sup>25</sup>R<sup>26</sup>, CONR<sup>25</sup>R<sup>26</sup>, NHR<sup>27</sup>, CO<sub>2</sub>R<sup>28</sup>, COR<sup>29</sup>, C(=NOH)R<sup>29</sup>,



or AD is CN, NR<sup>25</sup>R<sup>26</sup>, CONR<sup>25</sup>R<sup>26</sup>,

where R<sup>25</sup> and R<sup>26</sup> are either each independently H, C<sub>1-3</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl, C<sub>1-4</sub> alkylphenyl (each of which C<sub>1-3</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl and C<sub>1-4</sub> alkylphenyl are optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl and/or C<sub>1-4</sub> alkoxy, (each of which latter C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy is optionally substituted by one or more halogen)),

or R<sup>25</sup> and R<sup>26</sup> are taken together with the N atom to which they are attached and can form a 4- to 7-membered heterocyclic ring optionally incorporating one or more further hetero atoms selected from N, O and S, and which ring is optionally substituted by one or more C<sub>1-4</sub> alkyl, OH, =O, NO<sub>2</sub>, NH<sub>2</sub> and/or halogen,

R<sup>27</sup> is COR<sup>30</sup>, CO<sub>2</sub>R<sup>31a</sup>, SO<sub>2</sub>R<sup>31b</sup>,

R<sup>28</sup> and R<sup>29</sup> are each independently H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl and C<sub>1-4</sub> alkylphenyl are optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy (each of which latter C<sub>1-4</sub> alkyl and C<sub>1-4</sub> alkoxy are optionally substituted by one or more halogen),

R<sup>30</sup> is H, C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, aryl, aryloxy, C<sub>1-4</sub> alkylphenyl, phenyl(C<sub>1-4</sub>)alkoxy, (each of which C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, aryl, aryloxy, C<sub>1-4</sub> alkylphenyl and phenyl(C<sub>1-4</sub>)alkoxy are optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy (which latter alkyl and alkoxy are optionally substituted by one or more halogen)),

R<sup>31a</sup> and R<sup>31b</sup> are each independently C<sub>1-4</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl or C<sub>1-4</sub> alkylphenyl, each of which is optionally substituted by one or more NO<sub>2</sub>, halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy, each of which latter alkyl and alkoxy is optionally substituted by one more halogen

E is H,  $\text{CONR}^{32}\text{R}^{33}$ ,  $\text{CSNR}^{32}\text{R}^{33}$ ,  $\text{COR}^{34}$ ,  $\text{CO}_2\text{R}^{34}$ ,  $\text{COCH}(\text{R}^{34a})\text{NH}_2$ ,  $\text{R}^{35}$ ,  $\text{CH}_2\text{CO}_2\text{R}^{35a}$ ,  $\text{CHR}^{35b}\text{CO}_2\text{R}^{35a}$ ,  $\text{CH}_2\text{OCO}_2\text{R}^{35c}$ ,  $\text{CHR}^{35d}\text{OCO}_2\text{R}^{35c}$ ,  $\text{COCR}^{36}=\text{CR}^{37}\text{NH}_2$ ,  $\text{COCHR}^{36}\text{CHR}^{37}\text{NH}_2$ , or  $\text{PO}(\text{OR}^{38})_2$ ,

5

$\text{R}^{32}$  and  $\text{R}^{33}$  are each independently H,  $\text{C}_{3-10}$  alkylalkenyl,  $\text{C}_{3-7}$  cycloalkyl (optionally substituted by  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ),  $\text{C}_{1-10}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by  $\text{C}_{1-4}$  alkyl) or phenyl optionally substituted by  $(\text{X})_n$ ),

10

or  $\text{R}^{32}$  and  $\text{R}^{33}$  can be taken together with the N atom to which they are attached and can form a 5- to 8-membered heterocycle optionally comprising further hetero atoms selected from N, O and S, which heterocycle is optionally substituted by  $\text{C}_{1-4}$  alkyl, optionally substituted by one or more halogen,

15

$\text{R}^{34}$  is H,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ,  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH), or  $\text{C}_{1-6}$  alkyl (optionally substituted by one or more halogen,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), or phenyl (optionally substituted by  $(\text{X})_n$ ,  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH)),

20

$\text{R}^{34a}$  is H,  $\text{C}_{1-6}$  alkyl (optionally substituted by one or more halogen,  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), or phenyl (optionally substituted by  $(\text{X})_n$ ,  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH)),  $\text{C}_{4-7}$  cycloalkyl (optionally substituted by one or more  $\text{C}_{1-4}$  alkyl), phenyl (optionally substituted by  $(\text{X})_n$ ,  $\text{C}_{1-4}$  alkanoyloxy,  $\text{NR}^{32}\text{R}^{33}$ ,  $\text{CONR}^{32}\text{R}^{33}$  and/or OH) or a naturally occurring amino acid substituent,

25

$\text{R}^{35}$  is  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl (optionally substituted by one or more  $(\text{X})_n$ ,  $\text{C}_{1-4}$  alkanoyl,  $\text{NHR}^{32}$ ,  $\text{CON}(\text{R}^{32})_2$ , and/or OH),  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl (optionally substituted by one or more  $(\text{X})_n$ ,  $\text{C}_{1-4}$

30

alkanoyl,  $\text{NHR}^{32}$ ,  $\text{CON(R}^{32})_2$ , and/or OH)),  $\text{C}_{1-4}$  alkoxy( $\text{C}_{1-4}$  alkyl), phenyl( $\text{C}_{1-4}$ )alkyloxy( $\text{C}_{1-4}$ )alkyl, tetrahydropyranyl, tetrahydrofuranyl, cinnamyl or trimethylsilyl,

5  $\text{R}^{35a,b,c}$  and  $\text{d}$  are each independently H,  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl optionally substituted by one or more  $(\text{X})_n$  or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

10  $\text{R}^{36}$  and  $\text{R}^{37}$  each independently represent H,  $\text{C}_{3-6}$  alkylalkenyl,  $\text{C}_{4-7}$  cycloalkyl, phenyl optionally substituted by one or more  $(\text{X})_n$ , or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

15  $\text{R}^{38}$  is  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, phenyl optionally substituted by one or more  $(\text{X})_n$ , or  $\text{C}_{1-6}$  alkyl (optionally substituted by  $\text{C}_{4-7}$  cycloalkyl optionally substituted by one or more  $\text{C}_{1-4}$  alkyl, or phenyl optionally substituted by one or more  $(\text{X})_n$ ),

$\text{R}^2$  when taken alone is H or halogen;

20

or  $\text{R}^1$  and  $\text{R}^2$ , when attached to adjacent carbon atoms, can be taken together with the carbon atoms to which they are attached, and may represent  $\text{Het}^{1a}$ ;

25  $\text{Het}^{1a}$  is a heterocyclic group containing up to 4 heteroatoms selected from N, O and S, which may comprise up to 3 rings (and is preferably an optionally benzo-fused 5- to 7-membered heterocyclic ring) and which group is optionally substituted by one or more substituents independently selected from OH, =O, halogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy, which  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy groups can be 30 optionally substituted by one or more  $\text{C}_{3-6}$  cycloalkyl, aryl( $\text{C}_{1-6}$ )alkyl, which aryl group is optionally substituted by one or more halogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy and  $\text{C}_{1-4}$  haloalkoxy,

which latter C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy and C<sub>1-4</sub> haloalkoxy groups can be optionally substituted by one or more NR<sup>23</sup>R<sup>24</sup>, NR<sup>23</sup>S(O)<sub>n</sub>R<sup>24</sup>, NR<sup>23</sup>C(O)<sub>m</sub>R<sup>24</sup>, and if a S atom is present in a ring, it can be present as part of a -S-, S(O)- or -S(O<sub>2</sub>)-group,

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which R<sup>23</sup> and R<sup>24</sup> when taken alone independently represent H, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> haloalkyl,

or R<sup>23</sup> and R<sup>24</sup> can be taken together with the N atom to which they are attached, to form a 4- to 6-membered heterocyclic ring optionally comprising one or more further heteroatoms selected from, N, O, or S, and which heterocyclic ring is optionally substituted by one or more halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy and/or C<sub>1-4</sub> haloalkoxy groups,

R<sup>3</sup> is H, CN, halogen, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl, aryloxy, heteroaryl, saturated heterocycle, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup>, NY<sup>2</sup>WY<sup>1</sup>, C<sub>1-6</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, (each of which alkyl, alkenyl and alkynyl groups is optionally substituted by one or more CN, halogen, OH, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkyloxycarbonyloxy, C<sub>1-6</sub> alkanoyl, C<sub>1-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl, aryloxy, heteroaryl, saturated heterocycle, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> and/or NY<sup>2</sup>WY<sup>1</sup>),

R<sup>4</sup> is C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl or C<sub>3-10</sub> alkynyl each of which groups is linked to the N atom via a sp<sup>3</sup> carbon, and which is optionally substituted by one or more OH, CN, halogen, C<sub>1-6</sub> alkoxy (optionally substituted by aryl), aryloxy (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH, =O and/or NY<sup>2</sup>WY<sup>1</sup>), C<sub>1-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyloxy, C<sub>4-9</sub> cycloalkanoyl, aryl (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl (optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH, =O and/or NY<sup>2</sup>WY<sup>1</sup>), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, OH, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY<sup>1</sup>),

heterocycle (optionally benzo-fused and optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl(optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, OH, =O, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY<sup>1</sup>), heterocycloxy (optionally substituted by one or more halogen, C<sub>1-6</sub> alkyl(optionally substituted by one or more CN and/or halogen), C<sub>1-4</sub> alkoxy, OH, =O, C<sub>1-4</sub> haloalkoxy, and/or NY<sup>2</sup>WY<sup>1</sup>),  
5 adamantyl or ZBNR<sup>14</sup>R<sup>15</sup>,

Z is a direct bond, CO or S(O)<sub>n</sub> group,

10 B is (CH<sub>2</sub>)<sub>p</sub>,

R<sup>12</sup> and R<sup>13</sup> each independently represent H or C<sub>1-4</sub> alkyl,

or R<sup>12</sup> and R<sup>13</sup> can be taken together with the N atom to which they are attached to  
15 form a 4- to 7-membered heterocycle optionally comprising a further hetero moiety selected from NR<sup>16</sup>, O and/or S, and which is optionally substituted by one or more C<sub>1-4</sub> alkyl,

R<sup>14</sup> and R<sup>15</sup> each independently represent H, C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl, C<sub>3-10</sub> alkynyl, C<sub>3-8</sub>  
20 cycloalkyl, aryl or heteroaryl,

or R<sup>14</sup> and R<sup>15</sup> can be taken together with the N atom to which they are attached to form a 4- to 7-membered heterocycle optionally comprising a further hetero moiety selected from NR<sup>16</sup>, O and/or S, and which is optionally substituted by one or more C<sub>1-4</sub>  
25 alkyl,

R<sup>16</sup> is H, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, (C<sub>1-6</sub> alkylene)(C<sub>3-8</sub> cycloalkyl) or (C<sub>1-6</sub> alkylene)aryl,

30 R<sup>5</sup> and R<sup>8</sup> when taken separately are each independently H, C<sub>1-6</sub> alkyl,

R<sup>5</sup> and R<sup>8</sup> can be taken together with the carbon atoms to which they are joined to form a C<sub>3-8</sub> cycloalkyl ring,

R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup> and R<sup>10</sup> when taken separately are H,

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R<sup>5</sup> and R<sup>6</sup> or R<sup>7</sup> can be taken together with the carbon atoms to which they are joined to form a C<sub>3-8</sub> cycloalkyl ring,

X is halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkyl or C<sub>1-4</sub> haloalkoxy,

10

m is 1 or 2;

n is 0, 1 or 2;

15 

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

q is 0 or 1;

20 "Naturally occurring amino acid substituent" means the  $\alpha$ -substituent that occurs in any one of the following natural amino acids, glycine, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, tyrosine, histidine, serine, threonine, methionine, cysteine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, arginine or proline;

25 "Heteroaryl" represents an aromatic ring containing up to four heteroatoms independently selected from N, O and S, and if a S atom is present in the ring, it can be present as part of a -S-, S(O)- or -S(O)<sub>2</sub>- group, and which may be joined to the remainder of the compound via any available atom(s);

30 "Heterocycle" is a group containing 1, 2 or 3 rings, and which contains up to 4 ring heteroatoms selected from N, O and S and up to 18 ring carbon atoms;

"Aryl", including in the definitions of "aryloxy", etc., means a group comprising a phenyl ring and which may incorporate a further carbocyclic ring fused to said phenyl ring and which may be joined to the remainder of the compound via any available atom(s) (examples of such groups include naphthyl, indanyl, etc.);

5

"Alkyl", "alkenyl" and "alkynyl" groups can be linear or branched if the number of carbon atoms allows;

"Cycloalkyl" groups can be polycyclic if the number of carbon atoms allows;

10

or a pharmaceutically or veterinarily acceptable derivative or prodrug thereof.

2. A substance according to claim 1 wherein the "Ar" ring represents phenyl or pyridyl.

15

3. A substance according to any preceding claim wherein R<sup>1</sup> when taken alone is OH, CN, halogen, NO<sub>2</sub>, NH<sub>2</sub>, NY<sup>2</sup>WY<sup>1</sup> or Het<sup>1</sup>.

4. A substance according to any preceding claim wherein R<sup>2</sup> when taken alone is H.

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5. A substance according to claim 1 or 2 wherein R<sup>1</sup> and R<sup>2</sup> are taken together with the carbon atoms to which they are attached and represent an optionally benzo-fused 5- to 7-membered heteroaryl ring optionally substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl.

25

6. A substance according to any preceding claim wherein X is Cl.

7. A substance according to any preceding claim wherein n is 0 and q is 0.

8. A substance according to any preceding claim wherein R<sup>3</sup> is H, CN, or C<sub>1-6</sub> alkyl (optionally substituted by one or more halogen, OH, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonyl,

30

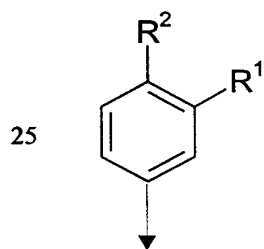
C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoyloxy, C<sub>2-6</sub> alkyloxycarbonyloxy, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> and/or NY<sup>2</sup>WY<sup>1</sup>).

9. A substance according to any preceding claim wherein R<sup>4</sup> is C<sub>1-10</sub> alkyl, C<sub>3-10</sub> alkenyl or C<sub>3-10</sub> alkynyl each of which groups is linked to the N atom via a sp<sup>3</sup> carbon, each of which is optionally substituted by C<sub>3-8</sub> cycloalkyl, aryl (optionally substituted by one or more methyl, ethyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, OH, =O, methoxy, OCF<sub>3</sub>), optionally benzo-fused heteroaryl (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, methoxy, OH, =O, OCF<sub>3</sub>), OH, aryloxy (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, OH, =O, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, methoxy, OCF<sub>3</sub>), CN, CF<sub>3</sub>, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyloxy, CONH(C<sub>3-8</sub> cycloalkyl), adamantyl, or (optionally benzo-fused) heteroaryloxy (optionally substituted by one or more methyl, halogen, CH<sub>2</sub>CN, CF<sub>3</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, OH, =O, methoxy, OCF<sub>3</sub>).

15

10. A substance according to any preceding claim wherein R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are each taken separately and are all H.

11. A substance according to any preceding claim wherein the "Ar" ring represents a group of formula:



12. A substance according to any preceding claim wherein R<sup>3</sup> is H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, i-C<sub>3</sub>H<sub>7</sub>, n-C<sub>3</sub>H<sub>7</sub> or CH<sub>2</sub>OCH<sub>3</sub>.

30



13. A substance according to any preceding claim except claim 5 wherein R<sup>1</sup> is OH, CN, I, Cl, NH<sub>2</sub>, NO<sub>2</sub>, optionally benzo-fused heteroaryl, NHSO<sub>2</sub>Y<sup>1</sup>, NHCOY<sup>1</sup> or NHCO<sub>2</sub>Y<sup>1</sup>.

5 14. A substance according to any preceding claim wherein R<sup>4</sup> is n-hexyl, 3-phenylpropyl, 3-phenyloxypropyl, 3-cyclohexylpropyl, 5-methylhexyl, 2-phenyloxyethyl, (4-cyanomethyl)benzyl, 2-cyclohexyloxyethyl, 2-benzyloxyethyl, 3-cyclohexylprop-2-en-1-yl, 2-(cyclohexylcarbonyl)ethyl, 3-(2-methylphenyl)propyl, 3-phenylprop-2-en-1-yl, 2-(indol-3-yl)ethyl, 3-cyclohexyl-3-hydroxypropyl, (indan-2-yl)methyl, 3-(4-fluorophenyl)propyl, 3-(thien-2-yl)propyl, 3-(thien-3-yl)propyl, 3-(pyrid-2-yl)propyl, 3-(3-methylthien-2-yl)propyl, 3-(thien-2-yl)prop-2-en-1-yl, 3-(thien-3-yl)prop-2-en-1-yl, 3-(pyrid-2-yl)prop-2-en-1-yl, 3-(3-methylthien-2-yl)prop-2-en-1-yl, 3-(3-methylpyrid-2-yl)prop-2-en-1-yl or 3-(2-methoxyphenyl)propyl.

15 15. A substance according to any preceding claim except claims 3, 4 and 13 wherein R<sup>1</sup> and R<sup>2</sup> are taken together with the carbon atoms to which they are attached are a 5-membered heteroaryl moiety optionally substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl.

16. A substance according to any preceding claim wherein R<sup>3</sup> is CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>.

20

17. A substance according to any preceding claim except claims 5 and 15 wherein R<sup>1</sup> when taken alone is OH, CN, I, Cl, NH<sub>2</sub>, NO<sub>2</sub>, 1,2,3-triazolyl, 1,2,4-triazolyl, imidazol-2-yl, pyridin-2-yl, thien-2-yl, imidazol-4-yl, benzimidazol-2-yl, NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl), NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl substituted by methoxy, CONH<sub>2</sub>, OH, CO<sub>2</sub>(C<sub>2-6</sub> alkyl), phthalimido, NH<sub>2</sub> or halogen), NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>NH(C<sub>1-6</sub> alkyl), NHSO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>, NHSO<sub>2</sub>Het<sub>1a</sub>, NHCO(C<sub>1-6</sub> alkyl) or NHCO<sub>2</sub>(C<sub>1-6</sub> alkyl).

25

18. A substance according to claim 17 wherein R<sup>1</sup> is OH, NHSO<sub>2</sub>CH<sub>3</sub>, NHSO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, NHSO<sub>2</sub>(n-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(i-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(n-C<sub>4</sub>H<sub>9</sub>), NHSO<sub>2</sub>NH(i-C<sub>3</sub>H<sub>7</sub>), NHSO<sub>2</sub>(N-methylimidazol-4-yl), NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OH, 1,2,4-triazolyl or imidazol-2-yl.

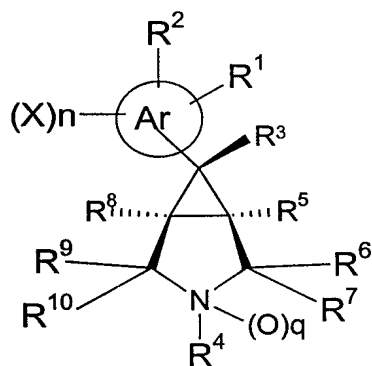
30

19. A substance according to claim 18 wherein  $R^1$  is OH,  $\text{NHSO}_2\text{CH}_3$ ,  $\text{NHSO}_2\text{C}_2\text{H}_5$  or imidazol-2-yl.

20. A substance according to claim 15 wherein  $R^1$  and  $R^2$  when taken together with the carbon atoms to which they are attached are an imidazole group optionally 2-substituted by  $\text{CF}_3$ .

21. A substance according to any preceding claim wherein  $R^4$  is n-hexyl, 3-phenylpropyl, (4-cyanomethyl)benzyl, 2-benzyloxyethyl, 3-cyclohexylprop-2-en-1-yl, 2-(indol-3-yl)ethyl, 3-(2-methylphenyl)propyl, 3-(4-fluorophenyl)propyl, 3-(pyrid-2-yl)propyl, 3-phenylprop-2-en-1-yl, 3-cyclohexyl-3-hydroxypropyl, 3-(thien-2-yl)propyl, 3-(thien-3-yl)propyl, 3-(3-methylthien-2-yl)propyl, 3-(thien-2-yl)prop-2-en-1-yl, 3-(thien-3-yl)prop-2-en-1-yl, 3-(pyrid-2-yl)prop-2-en-1-yl, 3-(3-methylthien-2-yl)prop-2-en-1-yl, 3-(6-methylpyrid-2-yl)prop-2-en-1-yl or 3-(2-methoxyphenyl)propyl.

22. A substance according to claim 1 which has the following relative stereochemistry:



23. A substance according to claim 1 which is selected from the compounds of the Examples as described herein, and the salts and prodrugs thereof.

24. A substance according to claim 23 selected from the compounds of the Examples 1, 5, 6, 10-13, 18, 20, 25-28, 32-34, 36, 38, 40, 42, 45, 47, 48, 57, 62, 67-69, 76, 79, 80, 84, 88, 90, 92, 97, 99, 102, 113, 114, 118, 119, 122-124, 136, 139 and 143, and the salts and prodrugs thereof.

5

25. A substance according to claim 24 selected from the compounds of the Examples 1, 5, 10, 12, 13, 26, 28, 36, 40, 45, 47, 48, 62, 68, 69, 79, 80, 84, 88, 90, 97, 99, 102, 113, 118, 114, 119, 122-124, 136, 139 and 143 described herein and the salts and prodrugs thereof.

10

26. A substance according to claim 25 selected from the compounds of the Examples 1, 10, 13, 26, 28, 62, 68, 69, 79, 80, 84, 88, 90, 97, 102, 113, 114, 118, 119, 12, 123, 124, 136, 139, and 143 described herein and the salts and prodrugs thereof.

15

27. A substance according to claim 26 selected from the compounds of the Examples 1, 10, 26, 79, 97, 102, 118, 139 and 143 described herein and the salts and prodrugs thereof.

28. A pharmaceutical or veterinary composition comprising a substance according to any one of the preceding claims, and a pharmacutically or veterinarily acceptable carrier.

20

29. A substance according to any of claims 1 to 27 for use in medicine.

25

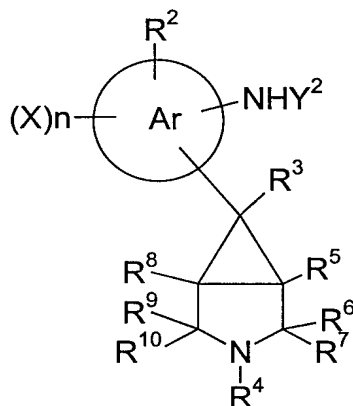
30. The use of a substance according to any one of claims 1 to 27 in the manufacture of a medicament for the treatment of a disease or condition mediated by opiate receptors.

30

31. A method of treatment of a condition mediated by an opiate receptor or receptors comprising administration of a therapeutically active amount of a substance according to any one of claims 1 to 27.

32. A process for the preparation of a substance according to claim 1 which comprises:

(a) for compounds of formula I in which q is 0 and  $R^1$  represents  $NY^2WY^1$ , reacting a compound of formula II,



II

with a compound of formula III,

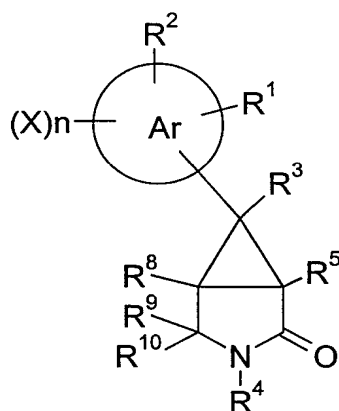


III

wherein  $Z^1$  is a suitable leaving group, such as halogen or  $Y^1SO_2O^-$ ;

(b) for compounds of formula I in which q is 0 and  $R^6$  and  $R^7$  both represent H,

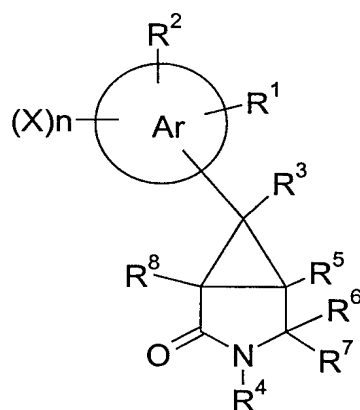
reduction of a compound of formula IV,



IV

using a suitable reducing agent;

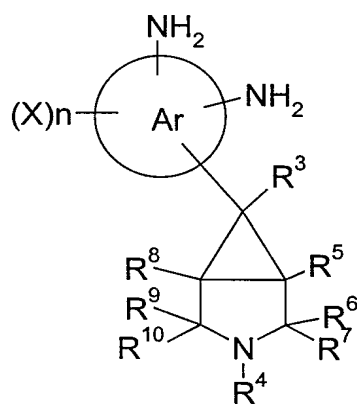
(c) for compounds of formula I in which q is 0 and  $R^9$  and  $R^{10}$  both represent H, reduction of a compound of formula V,



V

using a suitable reducing agent;

- (d) for compounds of formula I in which  $q$  is 0 and  $R^1$  and  $R^2$  are attached to adjacent carbon atoms and are taken together with the carbon atoms to which they are attached to represent  $\text{Het}^{1a}$ , in which  $\text{Het}^{1a}$  represents an imidazolo unit, reaction of a
- 5 corresponding compound of formula VI,



VI

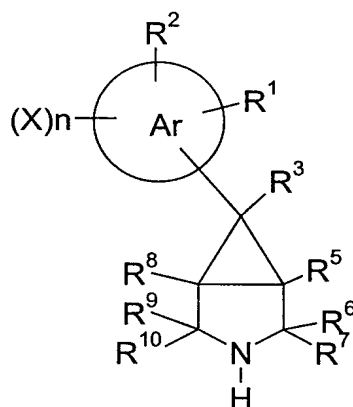
with a compound of formula VII,



VII

- 10 wherein  $R^y$  represents H or any of the optional substituents on  $\text{Het}^{1a}$  (as defined above), preferably H,  $\text{C}_{1-4}$  alkyl or  $\text{C}_{1-4}$  haloalkyl;

- (e) where  $q$  is 0, reacting a compound of formula VIII,



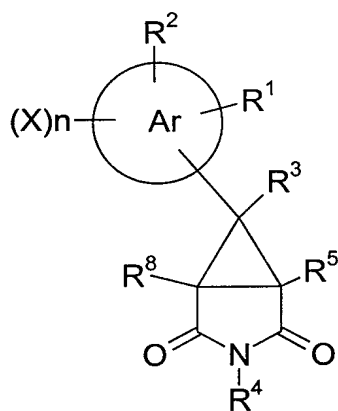
VIII

with a compound of formula IX,



wherein Lg is a leaving group;

- 5 (f) for compounds of formula I in which q is 0 and  $R^6$ ,  $R^7$ ,  $R^9$  and  $R^{10}$  are all H, reduction of a compound of formula X,



X

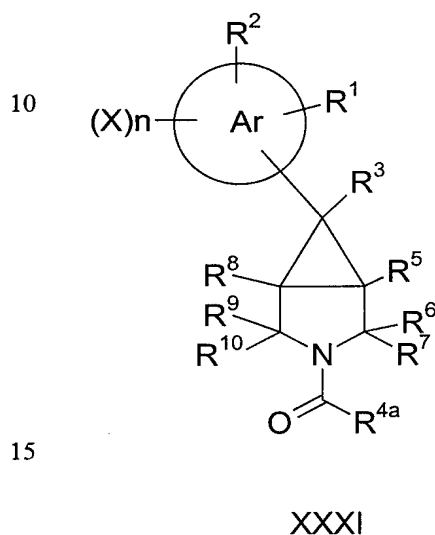
- 15 with a suitable reducing agent;

(g) for compounds of formula I in which q is 0 and  $R^1$  represents OH, reacting a compound of formula II, where  $Y^2$  is H, as defined above, with fluoroboric acid and isoamyl nitrite;

- (h) for compounds of formula I in which q is 0 and  $R^1$  represents Cl, reacting a  
20 compound of formula II, where  $Y^2$  is H, as defined above, with sodium nitrite in the

presence of dilute acid, followed by reaction with copper (I) chloride in the presence of concentrated acid;

- (i) for compounds of formula I in which q is 1, reacting a compound of formula I where q is 0 with a suitable oxidising agent such as aqueous hydrogen peroxide; or
- 5 (j) for compounds of formula I where q is 0, by reduction of a corresponding compound of formula XXXI,



where  $R^{4a}CH_2$  takes the same meaning as  $R^4$  as defined above,

- and where desired or necessary converting the resulting compound of formula I into a
- 20 pharmaceutically or veterinarily acceptable derivative or vice versa.

33. A compound of formula II, IV, V, VI, VIII, X,  $X^a$ , XI, XII, XIII, XIV, XXI, XXII, XXIII, XXIV, XXV, XXIX, XXIXa, XXX, XXXI as described herein.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 99/01852

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C07D209/52 A61K31/40 C07D401/12 C07D413/12 C07D403/10  
C07D403/04 C07D401/10 C07D409/10 C07D401/04 C07D409/06  
C07D405/06 C07D401/06 C07D417/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KARIN FRÖHLICH ET AL.: "Dealkylation of N(3)-methyl-6-mino-3-azabicyclo(3.1.0)hexane derivatives" TETRAHEDRON., vol. 54, - 22 October 1998 (1998-10-22) pages 13115-13128, XP002129438 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4020 * page 13125: compounds 8c, 9c and 20c; page 13126: compound 22c * * page 13127: compound 23c and 24c *	1
X	— —/—	33



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 February 2000

Date of mailing of the international search report

24/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H



## INTERNATIONAL SEARCH REPORT

 Int lional Application No  
 PCT/IB 99/01852

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RICHARD BALTZLY ET AL.: "Cyclopropanes derived from diaryldiazomethanes. II. 3-Azabicyclo(3.1.0)hexanes and their azaspiroquaternary salts" JOURNAL OF ORGANIC CHEMISTRY., vol. 27, - 1962 pages 213-218, XP002129439 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 * table III, compounds 36-43; table IV, compounds 44-47 *	1
X	* table II, compounds 13-30; table III, compound 35 *	33
X	DAVID A. BRENT ET AL.: "Field desorption mass spectrometry quaternary ammonium salts" TETRAHEDRON LETTERS., no. 42, - 1973 pages 4127-4130, XP002129440 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 * page 4128, compound I and III *	1
X	CHEMICAL ABSTRACTS, vol. 103, no. 2, 15 July 1985 (1985-07-15) Columbus, Ohio, US; abstract no. 11201z, MORITA, TOSHINOBU ET AL.: "Saponin composition of rhizomes of Panax japonicus collected in south Kyushu, Japan, and its significance in oriental traditional medicine." XP002129442 abstract & DATABASE CHEMICAL ABSTRACTS 'Online! CA 103:211201, compound with RN 1101-14-0 -& CHEM. PHARM. BULL., vol. 33, no. 9, - 1985 pages 3852-3858, XP002129441	1
A	EP 0 506 468 A (ELI LILLY AND COMPANY) 30 September 1992 (1992-09-30) cited in the application page 2 -page 3	1,28,30
A	EP 0 506 478 A (ELI LILLY AND COMPANY) 30 September 1992 (1992-09-30) cited in the application page 2 -page 3	1,10,30

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01852

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 31  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/01852

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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